2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of naphthalene and its two methylated derivatives, 1-methylnaphthalene and 2-methylnaphthalene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY- ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure - inhalation, oral, and dermal; and then by health effect - death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods - acute (14 days or less), intermediate (15 - 364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved- adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify

these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

It should be noted that there was only one study located that documented inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene. The exposure concentration for this study could not be determined from the information provided. Therefore, these compounds are not represented in Table 2-l or Figure 2-l. There was one study of oral exposure to 1-methylnaphthalene but no studies of 2-methylnaphthalene. The 1-methylnaphthalene study is included in Table 2-2 and Figure 2-2. There were no dermal studies of the toxicity of the methylnaphthalenes. Most of the data available on the toxicity of 1-methylnaphthalene and 2-methylnaphthalene are from studies that used the intraperitoneal and subcutaneous routes of compound administration. These studies are discussed in Section 2.4.

A User’s Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure.

2.2. Inhalation Exposure

2.2.1.1 Death

Two Greek infants died as a consequence of acute hemolysis that resulted from exposure to naphthalene-treated materials (clothing, diapers, blankets, rugs, etc.). Both infants exhibited a severe

form of jaundice (kemicterus) which often causes brain damage (Valaes et al. 1963). One infant suffered from a glucose-6-phosphate dehydrogenase (G6PD) deficiency. The other infant was apparently heterozygous for this trait. Individuals with a G6PD genetic defect are prone to hemolysis after exposure to a variety of chemical oxidizing agents including nitrates, nitrites, aniline, phenols (Dean et al. 1992), and naphthalene.

No studies were located that documented lethal effects in humans after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

Exposure to 78 ppm naphthalene for 4 hours did not cause any deaths in rats. In addition, no definitive adverse clinical signs were observed during the 14 days after exposure, and no gross pathologic lesions were observed at necropsy (Fait and Nachreiner 1985). A high background mortality in the male control group precluded drawing conclusions regarding the effects of lifetime exposures to 10 and 30 ppm naphthalene (6 hours/day 5 days/week) on lifetime mortality; no apparent effects on mortality occurred in the females (NTP 1992a).

No studies were located that documented lethal effects in animals after inhalation exposure to 1 -methylnaphthalene or 2-methylnaphthalene.

2.2.1.2 Systemic Effects

No studies were located that documented dermal effects in humans or animals after inhalation exposure to naphthalene. Most of the data on humans come from occupational and domestic settings where mothballs were the source of the naphthalene vapors. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1. No studies were located that documented systemic effects in humans or animals after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene except one study in animals that evaluated the hematological effects of both compounds.

Respiratory Effects. No studies were located that documented respiratory effects in humans after inhalation exposure to naphthalene.

TABLE 2-1. Levels of Significant Exposure to Naphthalene - Inhalation

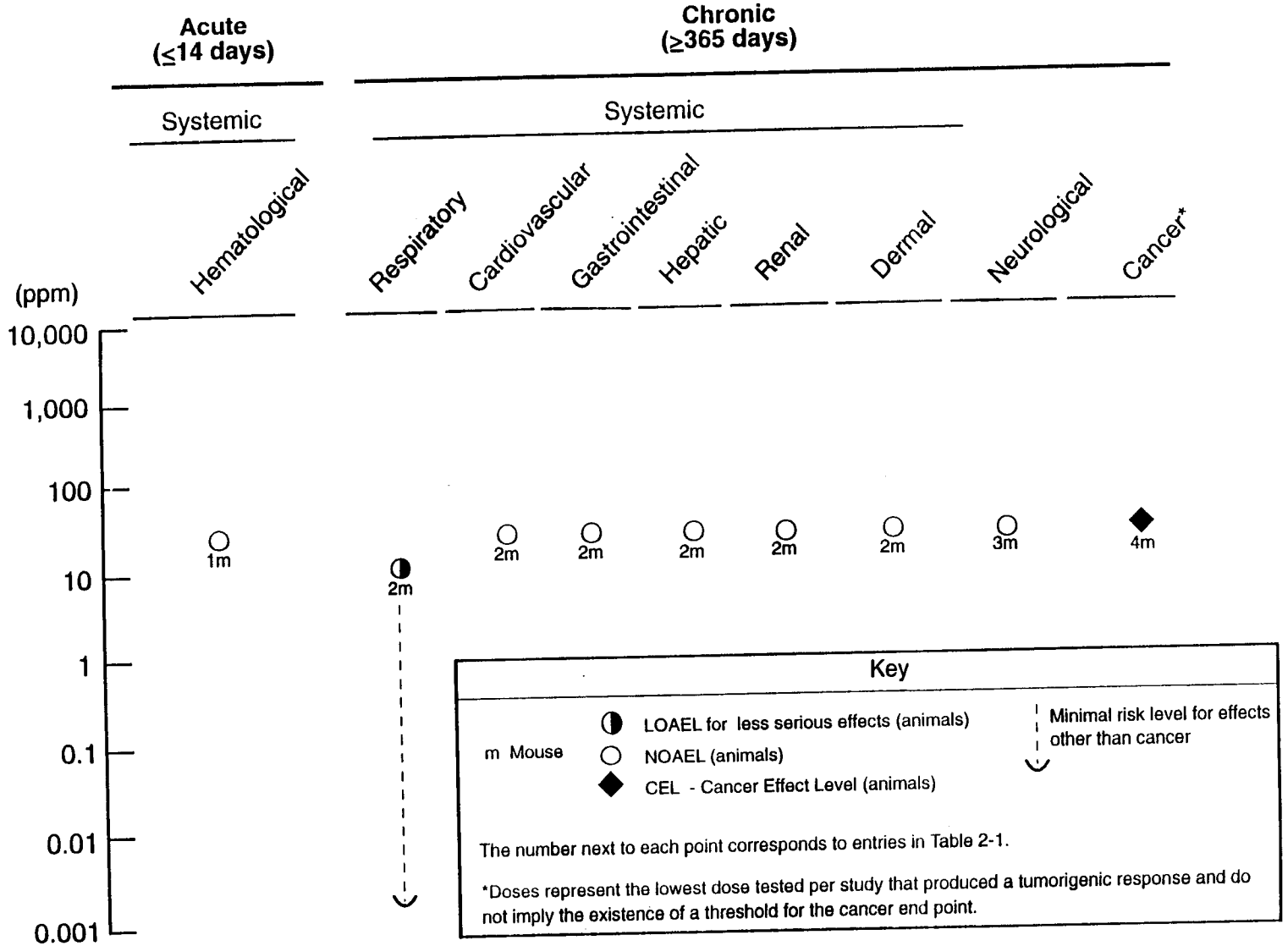
Key [a] to figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Systemic						
1	Mouse B6C3F1	14 d 5 d/wk 6 hr/d	Hemato	30			NTP 1992a
	CHRONIC EXPOSURE						
	Systemic						
2	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d	Resp		10 [b] (inflammation of the nose and lung, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium)		NTP 1992a
			Cardio	30			
			Gastro	30			
			Hepatic	30			
			Renal	30			
			Dermal	30			
	Neurological						
3	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d		30			NTP 1992a
	Cancer						
4	Mouse B6C3F1	104 wk 5 d/wk 6 hr/d				30 (pulmonary alveolar adenomas in females)	NTP 1992a

[a]The number corresponds to the entries in Figure 2-1.

[b]Used to derive a chronic inhalation Minimal Risk Level (MRL) of 0.002 ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; d = day(s); Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp =respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Naphthalene – Inhalation



Mice of both sexes showed chronic inflammation and metaplasia of the olfactory epithelium after inhalation of naphthalene vapors (10 and 30 ppm) for 2 years (NTP 1992a). Hyperplasia of the respiratory epithelium was also present in nearly all exposed mice and there was a dose-related increase in inflammatory lesions of the lungs. These data were used to calculate a chronic duration inhalation MRL for naphthalene as discussed in Table 2-l and shown in Figure 2-l. Other nonneoplastic lesions of the lungs were increased as compared to the controls, but no dose-related trend was noted.

According to recent guidance (EPA 1990b), a Human Equivalent Concentration (HEC) can be used to calculate MRLs for contaminants that are either reactive or soluble. In the mouse study used for MRL derivation, naphthalene exposure resulted in olfactory epithelial inflammation and metaplasia, respiratory epithelial hyperplasia, and granulomatous inflammation generally characterized as mild to moderate in severity. Because the authors considered the effects a generalized inflammation and repair process, naphthalene was not especially reactive in this study. Furthermore, with a water solubility of 31.7 mg/L at 20°C naphthalene cannot be considered particularly soluble. Consequently, the HEC methodology specified in EPA (1990b) cannot be applied. However, it should be noted that the end point of greatest concern in humans (Chematological dysfunction) may not have been adequately addressed in the NTP (1992a) study.

A change to mouth breathing occurred in rats during exposure to 78 ppm naphthalene but no other effects on respiration were noted (Fait and Nachreiner 1985).

Cardiovascular Effects. No studies were located that documented cardiovascular effects in humans after inhalation exposure to naphthalene. No histological changes were seen in the hearts of mice that were exposed to naphthalene (30 ppm) for 2 years (NTP 1992a).

Gastrointestinal Effects. Nausea, vomiting, and abdominal pain were reported in 8 adults and 1 child exposed to naphthalene vapors from large numbers of mothballs (300-500) scattered throughout their homes for odor and pest control (Linick 1983). Air samples collected in one home contained naphthalene at 20 parts per billion (ppb); concentrations could have been higher when the

mothballs were fresh. Gastrointestinal symptoms disappeared after the mothballs were removed. Few location-specific background data to support this air concentration were reported.

There were no histopathological changes in the stomach or intestines of mice exposed to naphthalene (30 ppm) for 2 years (NTP 1992a).

Hematological Effects. Hemolytic anemia is the most frequent manifestation of naphthalene exposure in humans. Acute hemolytic anemia was observed in 21 infants exposed to naphthalene via mothball-treated blankets, woolen clothes, or materials in the infants' rooms (Valaes et al. 1963). Ten of these children had a G6PD genetic defect that increased their sensitivity to hemolysis from a variety of chemicals, including naphthalene. Clinical observations included high serum bilirubin values, methemoglobin, Heinz bodies, and fragmented red blood cells. Inhalation appeared to be the primary route of exposure because in all children but two, the naphthalene-treated material was not worn next to the skin. One of the exceptions was an infant who wore diapers that had been stored in naphthalene.

Anemia was reported in 9 individuals exposed to large numbers of mothballs distributed throughout their homes (Linick 1983). The nature of the anemia and specific levels of naphthalene exposure were not identified. In one home, the naphthalene concentration was determined to be 20 ppb at the time of testing, but could have been higher when the mothballs were first distributed.

In another study, a woman who was exposed to reportedly high (but unmeasured) concentrations of a combination of naphthalene and paradichlorobenzene for several weeks in a hot, poorly ventilated work area developed aplastic anemia (Harden and Baetjer 1978). It is difficult to determine the contribution of naphthalene to the aplastic anemia since there was simultaneous exposure to paradichlorobenzene.

In animals, no treatment-related effects on hematologic parameters (hematocrit, hemoglobin concentration, erythrocyte counts, mean cell volume, reticulocytes, and leucocytes) were observed among mice exposed to 10 and 30 ppm naphthalene for 14 days (NTP 1992a). Due to high mortality in the control males, hematology measurements were not continued beyond 14 days.

The effects of 1-methylnaphthalene (pure and practical grade) and 2-methylnaphthalene (pure and practical grade) on the hematocrit values, total and differential white blood cell counts, and reticulocyte counts were determined in intact and splenectomized dogs. Each compound was dispersed in the atmosphere in a refined kerosene base using a fogger. Exposures occurred on four consecutive mornings (Lorber 1972). Based on the information presented, it was not possible to determine the exposure concentration.

Pure l-methylnaphthalene increased the reticulocyte counts in the splenectomized dogs but not the intact dogs. Reticulocyte values remained elevated for 10 days after the fogging ceased. Practical grade 1-methylnaphthalene increased leukocyte counts in intact and splenectomized dogs and neutrophil counts in intact dogs, but pure 1-methylnaphthalene had no effect on these parameters. 2-Methylnaphthalene had no effect on any of the parameters monitored (Lorber 1972).

Neither 1-methylnaphthalene nor 2-methylnaphthalene had an effect on hematocrit values, suggesting that these compounds do not appear to cause hemolysis under the conditions of the study. Since the increased reticulocyte counts were seen only in splenectomized dogs, it is difficult to interpret whether or not this change signifies increased hematopoiesis in response to 1-methylnaphthalene exposure (Lorber 1972).

Musculoskeletal Effects. No studies were located that documented musculoskeletal effects in humans after inhalation exposure to naphthalene.

Histological examination of the femur did not reveal compound-related effects in mice exposed to naphthalene at a concentration of 30 ppm for 2 years (NTP 1992a).

Hepatic Effects. Jaundice has been reported in infants and adults after exposure to naphthalene (Linick 1983; Valaes et al. 1963). However, the jaundice is a consequence of hemolysis rather than a direct effect of naphthalene on the liver. Infant exposures lasted l-7 days (Valaes et al. 1963); adult exposure durations were not provided (Linick 1983). Dose was not determined in either instance, although a concentration of 20 ppb was measured in the home of one affected individual (Linick 1983).

In animals, no treatment related gross or histopathological lesions of the liver were reported in mice exposed to 30 ppm naphthalene for 2 years (NTP 1992a).

Renal Effects. Renal disease was reported in 9 individuals (details not specified) exposed to large numbers of mothballs in their homes, but symptoms were not described and dose could not be determined (Linick 1983).

In animals, no treatment-related gross histopathological lesions of the kidneys were observed in mice exposed to 30 ppm naphthalene for 2 years (NTP 1992a).

Ocular Effects. Twenty-one workers exposed to naphthalene for up to 5 years in a plant that manufactured dye intermediates were examined for eye problems (Ghetti and Mariani 1956). During the period of exposure, plant conditions were primitive, involving heating of naphthalene in open vats and considerable worker contact with the naphthalene. Eight of the 21 workers developed multiple pin-point lens opacities which had no correlation with the age of the workers. These effects were not overtly noticeable and apparently had no effect on vision. They were judged to be a consequence of naphthalene exposure on the basis of their location in the crystalline lens and the fact that occurrence did not correlate with age. Exposure involved long-term inhalation of vapors and direct contact of vapors with the eyes and skin.

Retinal bleeding and the beginnings of a cataract were identified in a worker from a naphthalene storage area who was most likely exposed to naphthalene through inhalation and dermal/ocular contact (van der Hoeve 1906). The duration of exposure prior to seeking medical attention for eye irritation and problems with vision was not identified.

In animals, no treatment-related ocular lesions were observed in mice exposed to naphthalene at concentrations up to 30 ppm for 2 years (NTP 1992a). However, during a 4-hour exposure of rats to a concentration of 78 ppm, irritation to the eyes was evidenced through lacrimation.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located that documented immunological or lymphoreticular effects in humans or animals after inhalation exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

2.2.1.4 Neurological Effects

Infants are prone to permanent neurological damage (kernicterus) as a consequence of the jaundice that results from naphthalene-induced hemolysis. Bilirubin is absorbed by vulnerable brain cells and this leads to convulsions and sometimes death. Survivors often suffer from motor disturbances and mental retardation (McMurray 1977). Kernicterus was diagnosed in 8 of 21 Greek infants that experienced hemolysis as a result of naphthalene exposure (Valaes et al. 1963). Two of the eight died. One of the infants that died had no G6PD enzyme activity and the other had intermediate activity. Two of the infants were normal with regard to the G6PD trait. Of the remaining infants, three had no G6PD activity and the fourth had intermediate activity. Brain damage seldom occurs in adults as a consequence of jaundice (McMurray 1977).

Nausea, headache, malaise, and confusion were reported in several individuals (children and adults) exposed to large numbers of mothballs in their homes (Linick 1983). Actual levels and duration of exposure were unknown, although a concentration of 20 ppb was measured in one of the affected residences

No treatment-related histopathological lesions of the brain were reported in mice exposed to 30 ppm naphthalene for 2 years (NTP 1992a). This NOAEL is recorded in Table 2-l and plotted in Figure 2- 1.

No studies were located that documented neurological effects in humans or animals after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

2.2.1.5 Reproductive Effects

No studies were located that documented reproductive effects in humans after inhalation exposure to naphthalene, l-methylnaphthalene, or 2-methylnaphthalene.

In animals, histological examination did not reveal damage to male or female reproductive organs in mice exposed to 30 ppm naphthalene for 2 years (NTP 1992a).

No studies were located that documented reproductive effects in animals after inhalation exposure to 1 -methylnaphthalene or 2-methylnaphthalene.

2.2.1.6 Developmental Effects

No studies were located that documented developmental effects in humans or animals after inhalation exposure to naphthalene, l-methylnaphthalene, or 2-methylnaphthalene.

2.2.1.7 Genotoxic Effects

No studies were located that documented genotoxic effects in humans or animals after inhalation exposure to naphthalene, l-methylnaphthalene, or 2-methylnaphthalene. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located that documented carcinogenic effects in humans after inhalation exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

In animals, there was a statistically significant increase in the number of tumors per tumor-bearing mouse, but not in the number of mice with pulmonary adenomas after exposure to 10 or 30 ppm naphthalene vapors for 6 months (Adkins et al. 1986). However, the incidence of adenomas in the control group for this experiment was significantly lower than the pooled incidence observed in the control groups of eight concurrently conducted 6-month studies, and the difference in tumor incidence was not significantly greater than that of the historic controls.

In a 2-year bioassay (NTP 1992a), female (but not male) $B6C3F_1$ mice showed a significantly increased incidence in pulmonary alveolar/bronchiolar adenomas after a lifetime exposure to 30 ppm naphthalene vapors when compared to untreated controls. The incidence of tumors in the low dose

group (10 ppm) was less than the control level. On the basis of these data NTP (1992) determined that there was some evidence of naphthalene carcinogenicity in female mice.

No studies were located that documented carcinogenic effects in animals after inhalation exposure to 1-methylnaphthalene or 2-methylnaphthalene.

2.2.2 Oral Exposure

2.2.2.1 Death

Death has been documented in humans who intentionally ingested naphthalene. A 17-year-old male died 5 days after the ingestion of an unknown quantity of naphthalene mothballs. Death was preceded by vomiting, evidence of gastrointestinal bleeding, blood-tinged urine, and coma (Gupta et al. 1979). A 30-year-old female died following similar sequelae 5 days after reportedly swallowing 40 mothballs (25 were recovered intact from the stomach upon autopsy) (Kurz 1987). No studies were located that documented lethal effects in humans after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

Several animal studies have been conducted to estimate lethal doses of naphthalene. Mice appear to be more sensitive than rats or rabbits. The LD_{50} values in male and female mice were 533 and 710 mg/kg, respectively (Shopp et al. 1984). An LD_{50} of 354 mg/kg was estimated in female mice treated with naphthalene once daily by gavage for 8 consecutive days (Plasterer et al. 1985). The dose response curve appeared to be very steep because no deaths occurred at 250 mg/kg/day, but all animals died with a dose of 500 mg/kg/day. At the 300 mg/kg/day dose, mortality was approximately 15%. In a different study with a 14 day dosing period, 10% of the males and 5% of the females died at a dose of 267 mg/kg/day, but none were affected by doses of 27 and 53 mglkglday (Shopp et al. 1984).

The oral LD_{50} values in male and female rats were 2,200 and 2,400 mg/kg, respectively in one study (Gaines 1969), and 2,600 in a second study that did not differentiate by sex (Papciak and Mallory 1990). Male rats tolerated daily doses of 1,000 mg/kg without lethality, even after 18 days of administration (Yamauchi et al. 1986). In an increasing dose study, Germansky and Jamall (1988) treated male rats with naphthalene at doses beginning at 100 mg/kg/day and raised the dose weekly to

a final level of 750 mg/kg/day over 6 weeks. Doses were then kept constant for an additional 3 weeks. The animals tolerated 750 mg/kg/day with no mortalities. No increase in mortality was observed in rats administered naphthalene at 41 mg/kg/day in a 2-year feeding study (Schmahl 1955).

Although few data are available, rabbits appear to tolerate naphthalene in doses similar to those administered to rats. Two different rabbit strains were administered 1,000 mg/kg twice per week for 12 weeks without lethality (Rossa and Pau 1988).

Male and female mice survived oral exposure to concentrations of 71.6-143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). No studies were located that documented lethal effects in animals after ingestion of 1-methylnaphthalene.

All LOAEL values for lethality in each species after acute exposure to naphthalene are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located that documented musculoskeletal or dermal effects in humans or animals after oral exposure to naphthalene; data were available for all other systems. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located that documented systemic effects in humans after oral exposure to 1-methylnaphthalene or in humans or animals after exposure to 2-methylnaphthalene. The data from the one animal study of 1-methylnaphthalene are reported. The highest chronic NOAEL values and the lowest LOAEL value for systemic effects in mice are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No reports have been located to indicate that there are direct effects of oral exposure to naphthalene on the respiratory system in humans. In situations where respiratory effects such as hypoxia or pulmonary edema were noted, the respiratory effects appear to be secondary to hemolysis and the events leading to general multiple organ failure (Gupta et al. 1979; Kurz 1987). On hospital admission, one male infant was described as experiencing labored breathing after presumably

TABLE 2-2. Levels of Significant Exposure to Naphthalene and 1-Methylnapthalene - Oral

Key [a] to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (chemical form)
	ACUTE EXPOSURE						
	Death						
1	Rat Sherman	once (GO)				2200 M (LD50) 2400 F (LD50)	Gaines 1969
2	Rat Sprague-Dawley	once (GO)				2600 LD50	Papciak and Mallory 1990
3	Mouse CD-1	8 d 1x/d (GO)				300 (5/33 died)	Plasterer et al. 1985
4	Mouse CD-1	14 d 1x/d (GO)				267 (10/96 male, 3/60 female)	Shopp et al. 1984
5	Mouse CD-1	once (GO)				533 (LD50) 710 (LD50)	Shopp et al. 1984
	Systemic						
6	Human	once	Gastro		109 (adbominal pain)		Gidron and Leurer 1956
			Hemato			109 (hemolytic anemia)	
			Other			109 (106^{0} F fever)	
7	Rat Sprague-Dawley	9 d Gd 6-15 (GO)	Bd Wt	50 F		150 (31% decrease in maternal body weight gain)	NTP 1991a

TABLE 2-2 Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene - Oral (continued)

Key [a] to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg)	LOAEL Less serious (mg/kg)	LOAEL Serious (mg/kg)	Reference (chemical form)
8	Rat Sprague-Dawley	once (GO)	Resp		1000 lung lesions		Papciak and Mallory 1990
			Gastro		1000 stomach lesions		
9	Rat NS	10 d 1x/d (G)	Hepatic		1000 (39% increase in liver weight; increased lipid peroxidation, aniline hydroxylase activity)		Rao and Pandya 1981
			Renal	1000			
			Ocular	1000			
10	Mouse CD-1	14 d 1x/d (GO)	Resp	53 F 267 M	267 F (increased relative lung weight)		Shopp et al. 1984
			Hemato	267			
			Hepatic	267			
			Renal	267			
			Bd Wt	53	267 (4-10% decreased final body weight)		
11	Dog NS	once (F)	Hemato			1525 (hemolysis)	Zuelzer and Apt 1949
12	Rabbit NS	5 d (F)	Hepatic	2000			Srivastava and Nath 1969
			Ocular			2000 (cataracts)	
13	Rabbit NS	10 d 1x/d (GO)	Ocular			1000 (lens opacities, decreased ascorbic acid in aqueous humor)	van Heyningen and Pirie 1967

TABLE 2-2 Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene - Oral (continued)

Key [a] to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (chemical form)
	Immuno/Lymphor						
14	Mouse CD-1	14 d 1x/d (GO)		53	267 (30% decrease in thymus weight in males; 18% decrease in spleen weight in females)		Shopp et al. 1984
	Neurological						
15	Rat Sprague-Dawley	9d Gd 6-15 (GO)			50 [b] F (lethargy, slow breathing, increased rooting in adults)		NTP 1991a
16	Mouse CD-1	14 d (GO)		267			Shopp et al. 1984
	Reproductive						
17	Rat Sprague-Dawley	9 d Gd 6-19 (GO)		450			NTP 1991a
18	Mouse CD-1	8d Gd 7-14 (GO)				300 F (>10% maternal mortality)	Plasterer et al. 1985
19	Rabbit New Zealand white	14 d Gd 6-19 (GO)		120			NTP 1992b
	Developmental						
20	Rat Sprague-Dawley	9 d Gd 6-15 (GO)				150 F (decreased maternal corrected body weight gain >20%)	NTP 1991a

TABLE 2-2 Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene - Oral (continued)

Key [a] to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (chemical form)
21	Mouse CD-1	8d Gd 7-14 (GO)		300			Plasterer et al. 1985
22	Rabbit New Zealand white	14 d Gd 6-19 (GO)		120			NTP 1992b
23	Rabbit New Zealand white	13 d 1x/d Gd 6-18 (G)		40	200 F (maternal dyspnea, cyanosis, body drop, hypoactivity with no pathological aberrations)		PRI 1985, 1986
	INTERMEDIATE EXPOSURE						
	Systemic						
24	Rat Fisher 344	13 wk 5x/wk (GO)	Resp	400			Battelle 1980b
			Gastro		400 (intermittent diarrhea)		
			Hemato	200 M 400 F	400 M (increased neutrophils, decreased lymphocytes; marginal decreases in hematocrit and hemoglobin level)		
			Hepatic	400			
			Renal	200 M 400 F	400 M (10% had cortical tubular degeneration)		
			Ocular	400			
			Bd Wt		100 F (10-20% decreased body weight gain)	200 M (>20% decreased weight gain)	

TABLE 2-2 Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene - Oral (continued)

Key [a] to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (chemical form)
25	Rat blue spruce	9 wk 3.5d/wk (GO)	Resp	169			Germansky and Jamall 1988
			Hepatic		169 (elevated lipid peroxides)		
			Bd Wt			169 (20% decreased body weight gain)	
26	Rat Brown-Norway	4 wk 3.5d/wk (GO)	Ocular			500 (lens opacity)	Kojima 1992
27	Rat Sprague-Dawley Brown-Norway	6 wk	Ocular			500 M (cataract formation)	Murano et al. 1993
28	Rat black-hooded	79 d (GO)	Ocular			5000 (lens opacity)	Rathbun et al. 1990
29	Rat Brown-Norway	102 d NS (GO)	Ocular			700 (lens opacity)	Tao et al. 1991
30	Rat 5 strain.s	4-6 wk (GO)	Ocular			1000 (lens opacity)	Xu et al. 1992b
31	Rat Wistar	18 d 1x/d (G)	Hepatic		1000 (elevated lipid peroxides)		Yamauchi et al. 1986
			Ocular			1000 (cataracts)	

TABLE 2-2 Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene - Oral (continued)

Key [a] to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (chemical form)
32	Mouse B6C3F1	13 wk 5x/wk 1x/d (GO)	Resp	200			Battelle 1980a
			Cardio	200			
			Gastro	200			
			Hemato	200			
			Hepatic	200			
			Renal	200			
			Ocular	200			
33	Mouse CD-1	90 d 7d/wk 1x/d (GO)	Resp	133			Shopp et al. 1984
			Hemato	53 M 133 F	133 F (increase in hemoglobin, eosinophils, and activated partial thromboplastin time for females)		
			Hepatic		5.3 [c] M (decreased benzo(a)pyrene hydroxylase activity) 5.3 F (decreased BUN)		
			Renal	5.3 M 133 F	53 M (increased creatinine)		
34	Rabbit NS	5 wk	Ocular			500 M (destruction of retinal photoreceptors and vascularization of the retinal area)	Orzalesi et al. 1994

TABLE 2-2 Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene - Oral (continued)

Key to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (chemical form)
35	Rabbit Chinchilla Bastard New Zealand white	12 wk 2d/wk 1x/d (GO)	Ocular			1000 (cataracts)	Rossa and Pau 1988
36	Rabbit NS	4 wk 1x/d (GO)	Ocular		1000 (increased ascorbic acid in lens)		van Heyningen 1970
37	Rabbit NS	4 wk 1x/d (GO)	Ocular			1000 (lens opacities, retinal damage)	van Heyningen and Pirie 1967
	Immuno/Lymphor						
38	Rat Fisher 344	13 wk 5d/wk 1x/d (GO)			400 (lymphoid depletion of thymus)		Battelle 1980b
39	Mouse CD-1	90 d (GO)		133			Shopp et al. 1984
	Neurological						
40	Mouse B6C3F1	13 wk 5d/wk 1x/d (GO)		200			Battelle 1980a
41	Mouse CD-1	90 d (GO)		133			Shopp et al. 1984

TABLE 2-2 Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene - Oral (continued)

Key [a] to figure	Species/ strain	Exposure/ duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference (chemical form)
	Reproductive						
42	Mouse B6C3F1	13 wk 5d/wk 1x/d (GO)		200			Battelle 1980a
	CHRONIC EXPOSURE						
	Systemic						
43	Mouse B6C3F1	81 wk (F)	Resp		71.6 [d] M (alveolar proteinosis)		Murata et al. 1993 (1-MN)
			Cardio	143.7 F			
			Gastro	143.7 F			
			Hemato	140.2 M	75.1 F (increased hemoglobin, MCH, MCHC)		
			Hepatic	143.7 F			
			Renal	143.7 F			
			Endocr	143.7 F			
			Bd Wt	143.7 F			

[a]The number corresponds to the entries in Figure 2-2.

[b]Used to derive an acute oral Minimal Risk Level (MRL) of 0.05 mg/kg/day for naphthalene; dose was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

[c]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.02 mg/kg/day for naphthalene; dose was divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

[d]Used to derive a chronic oral Minimal Risk Level (MRL) of 0.07 mg/kg/day for 1-methylnaphthalene; dose was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = females; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); (GO) = gavge oil; Hemato = hematological; hr = hour(s); Immuno/Lymphor = imunological/lymphorecticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = males; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp =respiratory; wk = week(s); x = time(s); 1-MN = 1-methylnaphthalene

Figure 2-2. Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene – Oral

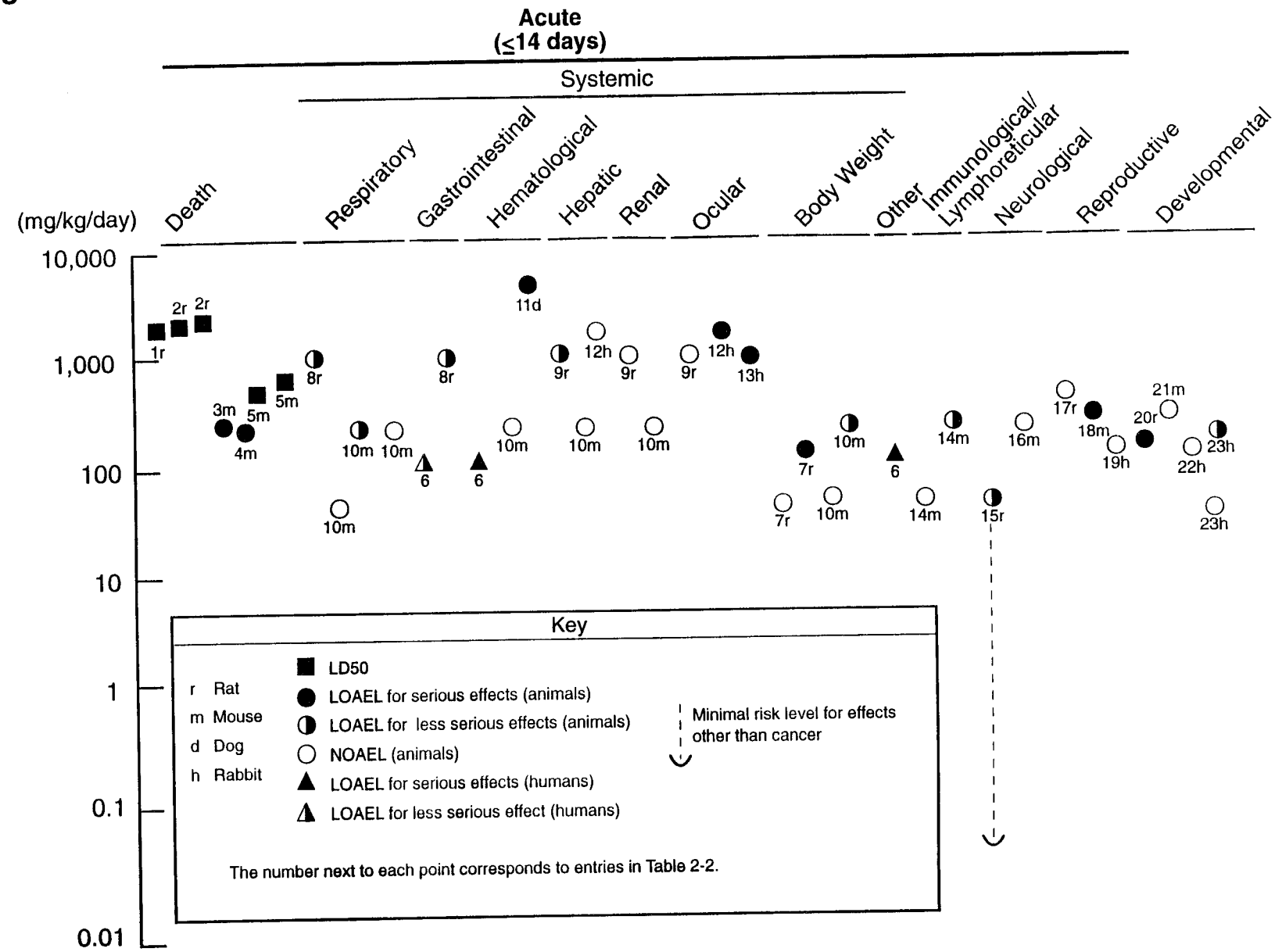


Figure 2-2. Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene – Oral (continued)

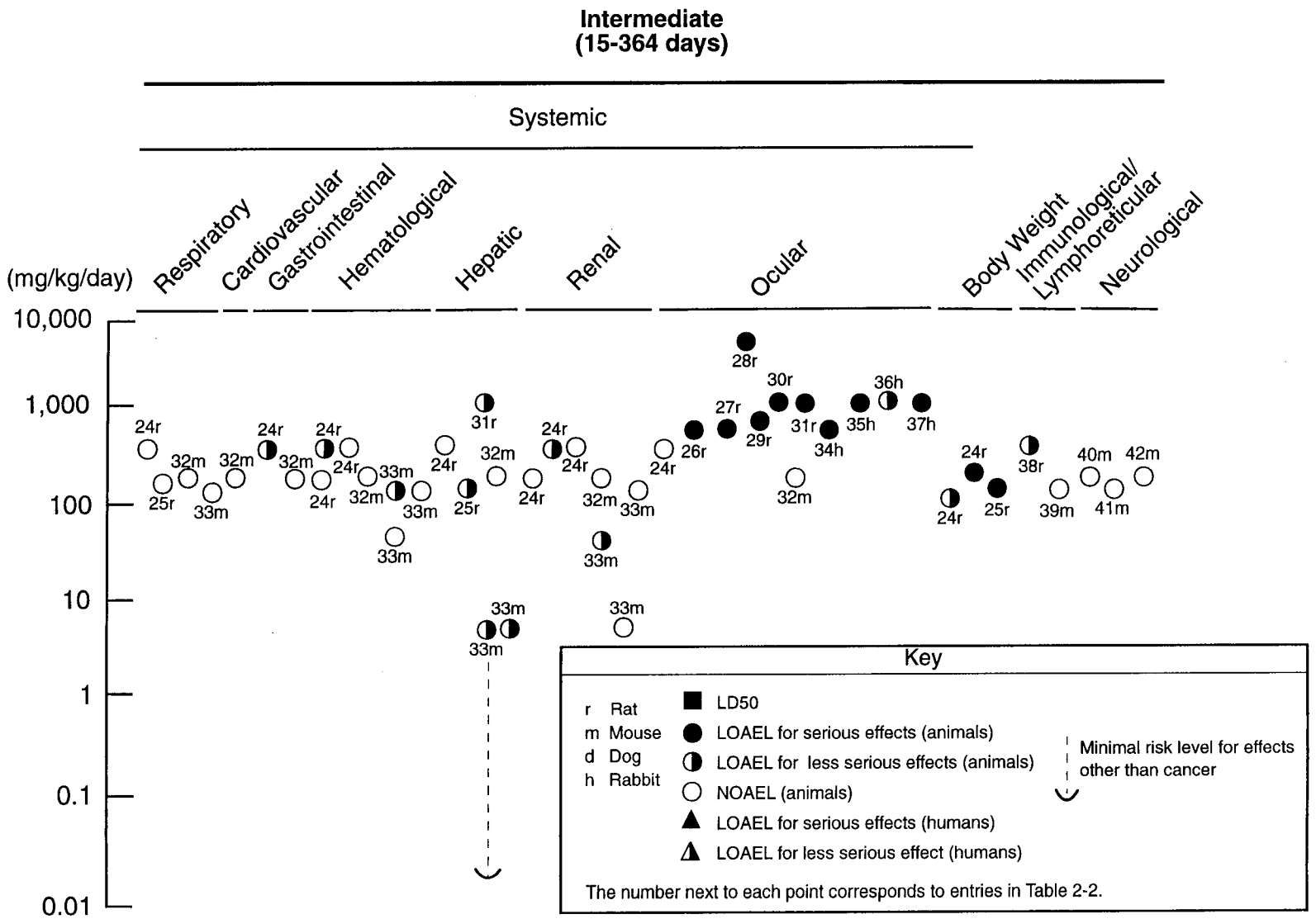
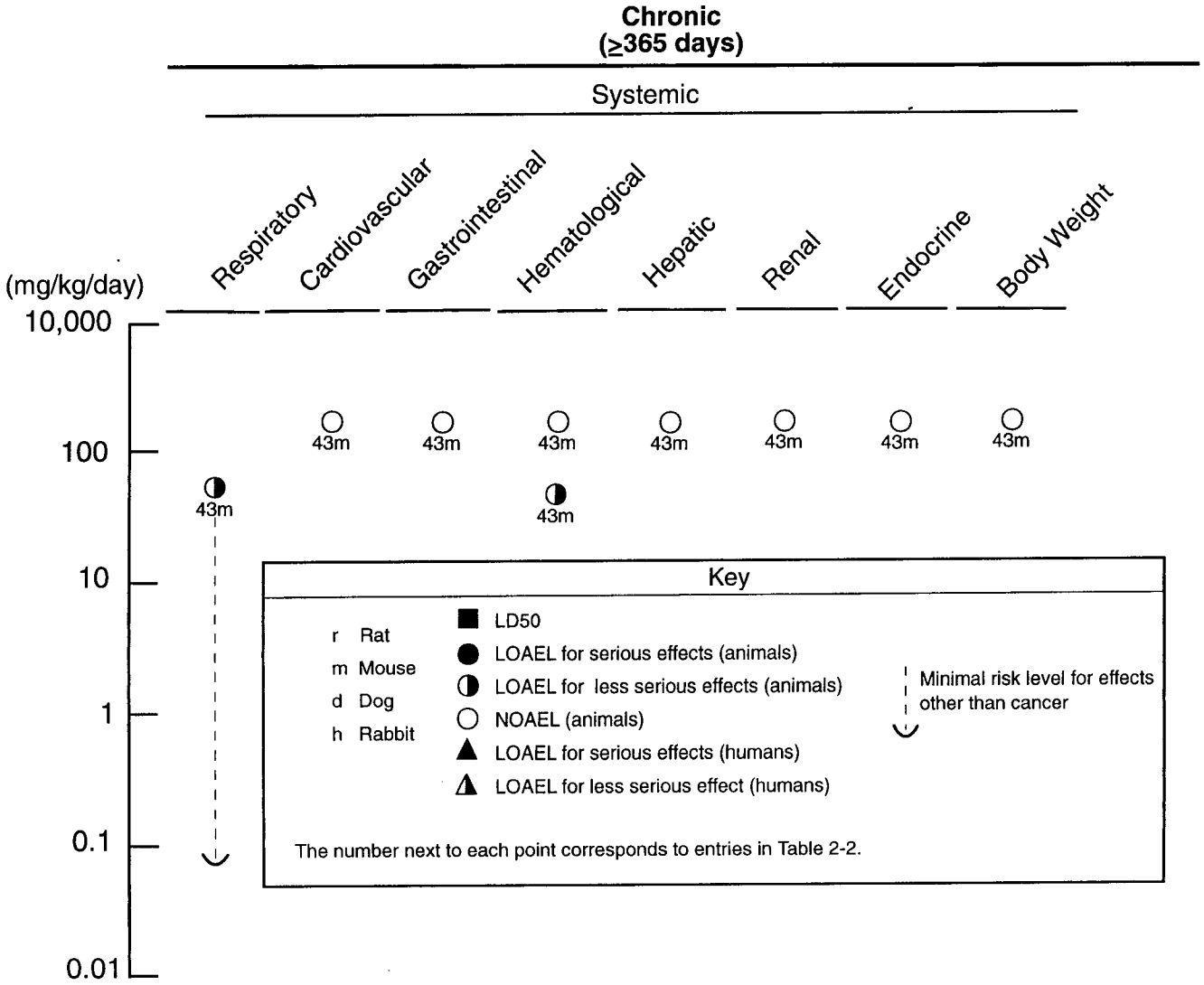


Figure 2-2. Levels of Significant Exposure to Naphthalene and 1-Methylnaphthalene – Oral (continued)



chewing a naphthalene-containing diaper pail deodorant block (Haggerty 1956). This may have been a reflection of the reduced oxygen carrying capacity of the blood due to hemolysis.

Lesions of the lungs were seen in rats that died after being given a single large dose of naphthalene (1,000-4,000 mg/kg) during an LD,, study (Papciak and Mallory 1990). On the other hand, no significant respiratory toxicity was seen in rats following oral administration of naphthalene at time-weighted average doses of 169 mg/kg/day for 9 weeks (Germansky and Jamall 1988). Dosages were increased from 100 to 750 mg/kg/day over a 6-week period and held constant at 750 mg/kg/day for the last 3 weeks of the 9-week exposure period.

Lung weights were increased in female mice administered naphthalene at 267 mg/kg/day for 14 days; however, these effects were not seen in either sex at 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the lungs were noted in mice at doses up to 200 mg/kg/day (Battelle 1980a) or in rats at doses of 400 mg/kg/day (Battelle 1980b) after 13 weeks of exposure.

There was significantly increased incidence in nodular clusters of alveolar proteinosis in the lungs of male and female $B6C3F_1$ mice fed diets containing 1-methylnaphthalene (71.6 mg/kg/day or 75.1 mg/kg/day, respectively) for 81 weeks (Murata et al. 1993). The lesions contained acidophilic amorphous material, foam cells, and cholesterol crystals. There was no apparent inflammation, edema, or fibrosis of the tissues. This effect was used as the basis of the chronic oral MRL for 1 -methylnaphthalene (0.07 mg/kg/day).

Cardiovascular Effects No studies were located that demonstrate any direct effects of naphthalene ingestion on the cardiovascular system. In those reports where cardiovascular effects such as increased heart rate and decreased blood pressure were noted in humans, the cardiovascular effects appeared to be secondary to the hemolytic effects and the events leading to general multiple organ failure (Gupta et al. 1979; Kurz 1987).

No gross or histopathological lesions of the heart were noted in mice at doses up to 200 mg/kg/day (Battelle 1980a) or in rats at doses of 400 mg/kg/day (Battelle 1980b) after 13 weeks of exposure.

Heart weights were significantly decreased (6-7%) in male and female mice who were fed 1-methylnaphthalene for 81 weeks in their diet. However, the changes in heart weight were not dose-related and there were no accompanying tissue abnormalities (Murata et al. 1993).

Gastrointestinal Effects. Gastrointestinal disorders are common following naphthalene ingestion by humans These effects have been attributed to the irritant properties of naphthalene (Kurz 1987). Nausea, vomiting, abdominal pain, and diarrhea (occasionally containing blood) have been reported (Bregman 1954; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985). While the presence of blood in the stool is indicative of intestinal bleeding, only a few areas of mucosal hemorrhage were noted in postmortem examination of the intestines (Kurz 1987). These areas were restricted to the small bowel and colon. No frank erosions or perforations were noted anywhere in the gastrointestinal tract.

A single dose of 1,000-4,000 mg/kg was associated with stomach lesions and discoloration of the intestines in rats who died during an LD_{50} study. The survivors were not affected (Papciak and Mallory 1990). No gross or histopathological lesions of the stomach, small intestine, and colon were noted in mice at doses of up to 200 mg/kg/day (Battelle 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (Battelle 1980b). There was some intermittent diarrhea in the rats but this may not have been treatment related.

No histopathological lesions were seen in the stomach or intestines of mice fed 71.6-143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993).

Hematological Effects. The most common hematologic effect in humans following the ingestion of naphthalene is hemolytic anemia (Dawson et al. 1958; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Mackell et al. 1951; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Shannon and Buchanan 1982). Changes observed in hematology and blood chemistry are consistent with this effect: hemolysis, decreased hemoglobin and hematocrit values, increased reticulocyte counts, serum bilirubin levels, and Heinz bodies. This was caused by hemolysis. Most of the reported case studies provide no information on dose. However, in one case report, a 16-year-old girl swallowed 6g of naphthalene before exhibiting hemolytic anemia (Gidron and Leurer 1956). This is a dose of 109 mg/kg (assuming a 55-kg body weight). The hematological condition of this individual, who was an immigrant from Kurdistan, was not provided.

As mentioned previously, there is an association between G6PD deficiency and the hemolytic effects of naphthalene (Dawson et al. 1958; Melzer-Lange and Walsh-Kelly 1989; Shannon and Buchanan 1982). Individuals with a genetic defect for this enzyme show an increased susceptibility to hemolysis from naphthalene exposure.

Few hematologic changes have been reported in animals. Standard laboratory animals do not appear to be sensitive to the hemolytic effects of naphthalene. In CD-l mice, naphthalene at doses up to 267 mg/kg/day for 14 days or up to 133 mg/kg/day for 90 days did not result in hemolytic anemia (Shopp et al. 1984). However there was an increase in eosinophils in the 16day and 90-day studies. There was an increase in prothrombin time at 14 days. The clinical significance of these observations is not clear.

There were no pronounced changes in red cell related hematological parameters in mice following 13-week exposures to doses of up to 200 mg/kg/day (Battelle 1980a) and up to 400 mg/kg/day in rats (Battelle 1980b). In male mice exposed to 200 mg/kg/day for 13 weeks there was a decrease in segmented neutrophils and an increase in lymphocytes, but in male rats given 400 mg/kg/day there were increased neutrophils and decreased lymphocytes. These effects were not considered by the authors to be biologically significant.

Hemolytic anemia was reported by Zuelzer and Apt (1949) in a dog receiving a single 1,525 mg/kg dose of naphthalene in food and in another dog receiving approximately 263 mg/kg/day for 7 days in food. Dogs are more susceptible to chemically induced hemolysis than are rats and mice.

Exposure to 75.1 mg/kg/day or 143.7 mg/kg/day 1-methylnaphthalene for 81 weeks was associated with a slight but significant increase in the hemoglobin concentration, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration in female mice (Murata et al 1993). Corresponding changes were not observed in males given comparable doses. Given the rodent’s apparent lack of sensitivity to the hemolytic effects of naphthalene, the implications of the female mouse hematological results for human health assessment are unknown. Nevertheless, these hematological findings may have significance, given that hemolytic anemia is an end point of concern in naphthalene-exposed humans (Harden and Baetjer 1978; Linick 1983).

Hepatic Effects. Evidence of hepatotoxicity following oral exposure to naphthalene has been reported in humans, based on elevated plasma levels of hepatic enzymes (such as aspartate aminotransferase and lactic acid dehydrogenase) (Kurz 1987; Bjwang et al. 1985), and liver enlargement (Gupta et al. 1979; MacGregor 1954). The relationship between liver enlargement and potential naphthalene-induced hemolysis is unknown

There is limited evidence of hepatic effects in laboratory animals. A 39% increase in liver weight, a modest elevation in activity of aniline hydroxylase and evidence of lipid peroxidation were observed in male rats treated with naphthalene at 1,000 mg/kg/day for 10 days (Rao and Pandya 1981). Male rats demonstrated an elevation in hepatic lipid peroxides at naphthalene doses of 1,000 mg/kg/day for 18 days (Yamauchi et al. 1986). In rats administered increasing doses of naphthalene up to 750 mg/kg/day (time-weighted average 169 mg/kg/day), hepatic lipid peroxides were doubled at the end of 9 weeks of treatment (Germansky and Jamall 1988).

No effects on liver weight were observed in male or female mice receiving naphthalene at doses up to 267 mg/kg/day for 14 days or male mice receiving 133 mg/kg/day for 90 days (Shopp et al. 1984). Liver weights were significantly increased in females receiving 133 mg/kg/day naphthalene for 90 days. No gross or histopathological lesions of the liver were noted in mice at doses of up to 200 mg/kg/day (Battelle 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (Battelle 1980b).

Blood urea nitrogen (BUN) values were significantly decreased as compared to the controls in the females at all doses. Although a dose-response pattern was evident for the decrease in BUN, the BUN values for each group were within normal ranges for this species. However, the BUN/creatinine ratio for all the exposed females was about 33% lower than the corresponding values for either the concurrent of the vehicle control. There were no significant differences in the BUN values for the males, but the BUN/creatinine values for the mid- and high-dose males were lower than the values for the concurrent or vehicle controls. These results suggest that naphthalene could have inhibited protein catabolism or the metabolism of nitrogen through the urea cycle (a hepatic pathway). Furthermore, statistically significant and dose-related inhibition of benzo(a)pyrene hydroxylase activity occurred in males and females starting at 5.3 and 53 mg/kg/day, respectively. These effects were used as the basis of an intermediate duration oral MRL of 0.02 mg/kg/day for naphthalene (Shopp et al. 1984).

There was a statistically significant decrease in the activity of benzo(a)pyrene hydroxylase activity at doses of 53 and 133 mg/kg/day in mice exposed to naphthalene for 90 days and an increase in aniline hydroxylase activity with a dose of 133 mg/kg/day (Shopp et al. 1984). These changes may be a reflection of a minimal impact of naphthalene on liver function.

There were no changes in liver weights or tissue histopathology in male or female mice who consumed 71.6-143.7 mg/kg/day 1-methylnaphthalene in their diets for 81 weeks (Murata et al. 1993).

Renal Effects. Renal toxicity has been reported in case studies of humans who ingested naphthalene. Frequent findings include the elevation of creatinine and blood urea nitrogen and the presence of proteinuria and hemoglobinuria (Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985; Zuelzer and Apt 1949). The presence of blood in the urine and increased concentrations of urobilinogen are a consequence of acute hemolysis and do not reflect any direct action of naphthalene on the kidney. Oliguria (Kurz 1987) and anuria (Gupta et al. 1979) were noted in two case reports, although urine output was normal in a third (Ojwang et al. 1985). Painful urination with swelling of the urethral orifice was also associated with medicinal naphthalene ingestion (Lenzenius 1902). Proximal tubule damage and general tubular necrosis were found in postmortem examinations of two individuals who died following naphthalene ingestion (Gupta et al. 1979; Kurz 1987).

Renal effects were not consistently observed in animals exposed orally to naphthalene. Following 10 days of exposure of rats to naphthalene at 1,000 mg/kg/day, no changes were noted in kidney weight, lipid peroxidation, or in the activity of alkaline phosphatase and aniline hydroxylase (Rao and Pandya 1981). No changes were observed in the kidney weights of mice administered naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the kidney were noted in mice at doses of up to 200 mg/kg/day (Battelle 1980a) or in rats at doses of up to 200 mg/kg/day after 13 weeks of exposure (Battelle 1980b). In the male rats, 10% showed cortical tubular degeneration that may have been compound-related at a dose of 400 mg/kg/day (Battelle 1980b).

Relative kidney weights were increased slightly in male mice fed diets containing 71.6 or 140.2 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The females were not affected and there were no histopathological lesions in the males or females.

Ocular Effects. In an early report of naphthalene toxicity, a 36-year-old pharmacist who ingested an unspecified amount of unpurified naphthalene in a castor oil emulsion over a 13-hour period as treatment of an intestinal disorder became nearly blind 8 or 9 hours later (Lezenius 1902). A medical examination the following month revealed constricted visual fields associated with optic atrophy and bilateral zonular cataracts. At 1.5 meters the patient's vision was limited to finger counting. Impurities in the naphthalene probably contributed to the symptoms observed (Grant 1986).

Several animal studies have demonstrated ocular changes following oral naphthalene exposure. Within 1 week following exposure to naphthalene (500 or 1,000 mg/kg/day), lens densities were increased in rats and cataracts developed within 4 weeks (Kojima 1992; Murano et al. 1993; Yamauchi et al. 1986). Eight rabbits (strain not identified) all developed cataracts during oral administration of naphthalene at 2,000 mg/kg/day for 5 days (Srivastava and Nath 1969). Cataracts began to develop by the first day after a single 1,000 mg/kg naphthalene dose in 3 Chinchilla Bastard rabbits (Rossa and Pau 1988). In the solitary New Zealand white rabbit tested, cataracts began to develop after administration of four 1,000 mg/kg doses (dosing 2 times/week) and maximized after 12 weeks (Rossa and Pau 1988).

When naphthalene was administered orally at 1,000 mg/kg/day for up to 28 days, cataracts developed in 10 of 16 Dutch (pigmented) rabbits and in 11 of 12 albino rabbits (Van Heyningen and Pirie 1976). Lens changes were seen as early as day 2 of exposure. The authors noted that albino strains were more likely to develop cataracts over a 4-week course of treatment at 1,000 mg/kg/day than pigmented strains such as the Dutch rabbit.

In contrast, administration of a time-weighted-average 500-mg/kg/day dose of naphthalene in corn oil by gavage for 6 weeks resulted in more rapid development of cataracts in pigmented Brown-Norway rats than in nonpigmented Sprague-Dawley rats (Murano et al. 1993). Cataracts developed in three distinct phases. In the first phase, water clefts formed in the anterior subcapsular region of the eye. The second stage was the development of a semicircular opaque area in the lens, and the last stage was the appearance of a wedge-shaped opacity that could be seen with retroillumination and a wide, zonular-ring opacity that was seen with slit imaging. Each stage occurred about 1 week earlier in the Brown-Norway rats than in the Sprague Dawley rats. The first stage began 1 week after treatment was initiated in the Brown-Norway rats, and stage three cataracts were seen in all animals by the end of the 6 weeks. Progressive development of lens opacities was also reported in rats that were exposed to 700 or 5,000 mg/kg/day naphthalene by gavage for 79-102 days (Rathburn et al. 1990; Tao et al. 1991).

Damage to the eyes with continued exposure to naphthalene is not limited to lens opacification (Orzalesi et al. 1994). Retinal damage was noted in pigmented rabbits given time-weighted-average doses of 500 mg/kg/day naphthalene in corn oil by gavage for 5 weeks The first changes to the retina occurred at about 3 weeks with degeneration of the photoreceptors. There was a subsequent increase in the retinal pigment epithelium as these cells phagocytized the debris from the photoreceptors. By the end of 6 weeks, the photoreceptor layer had almost entirely disappeared and was replaced with fibroglial tissue. As damage progressed, there was dense subretinal neovascularization of the area.

A number of biochemical changes were seen in the eyes after acute and intermediate naphthalene exposures After 1 week of treatment with 1,000 mg/kg/day, glutathione levels in the lens were decreased in rats (Xu et al. 1992b; Yamauchi et al. 1986). After 30 days of treatment with doses of 5,000 mg/kg/day, total glutathione levels were reduced by 20% (Rathbun et al. 1990), and there was a 22% reduction at 60 days with a dose of 700 mg/kg/day (Tao et al. 1991). At 60 days, glutathione peroxidase activity in the lens was decreased by up to 45% and there was a 20-30% decrease in glutathione reductase activity (Rathbun et al. 1990). Comparable decreases in the activities of both enzymes were seen at 102 days with lower naphthalene doses (Tao et al. 1991). No changes were observed in the activity of glutathione synthetase or gamma-glutamyl cysteine synthetase (Rathbun et al. 1990). After 4 weeks of compound treatment (500 mg/kg/day) the activities of aldose reductase, sorbitol dehydrogenase, lactic dehydrogenase, and glutathione reductase were lower than in controls (Kojima 1992). No changes in ocular lipid peroxides were reported when male Blue Spruce pigmented rats were administered incremental doses of naphthalene which peaked at 750 mg/kg/day for 9 weeks (Germansky and Jamall 1988). Lens and capsule LDH activities were greatly reduced in rabbits while o-diphenyl oxidase activity was elevated with a dose of 2,000 mg/kg/day for 5 days (Srivastava and Nath 1969).

In a 2-year rat feeding study, no eye damage was seen at a naphthalene dosage of 41 mg/kg/day (Schmahl 1955). The details of the eye examination were not provided.

Body Weight Effects. No studies were located that documented effects on body weight in humans after oral exposure to naphthalene.

After 13 weeks, there were decreased body weight gains in rats with exposure to 100 mg/kg/day naphthalene and greater (Battelle 1980b). Mice exposed to 267 mg/kg/day for 14 days also showed a decreased body weight gain (Shopp et al. 1984).

There was no significant difference between body weights of mice who were given up to 143.7 mg/kg/day 1-methylnaphthalene in their diets and those of the control animals throughout an 81-week exposure period (Murata et al. 1993).

Other Systemic Effects. Several humans who consumed naphthalene experienced elevated body temperatures which may have been related to their hemolytic crisis (Chusid and Fried 1955; Gidron and Leurer 1956; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985). However, in some situations, bacterial infections rather than hemolysis may have been the cause of the fever (Kurz 1987; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Zuelzer and Apt 1949).

No studies were located that documented other systemic effects in animals after oral exposure to naphthalene.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located that documented immunological or lymphoreticular effects in humans after oral exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. However, an enlarged spleen is a frequent consequence of hemolysis and was noted in the postmortem examination of one human subject who died after ingesting a large quantity of naphthalene (Kurz 1987).

Mice treated with naphthalene at oral doses as high as 267 mg/kg/day for 14 days showed no effects on humoral immune responses, delayed hypersensitivity responses, bone marrow stem cell number, or bone marrow DNA synthesis (Shopp et al. 1984). Mitogenic responses to concanavalin A (but not to lipopolysaccharide) were reduced in high dose females only. None of these effects were noted at doses of 27 or 53 mg/kg/day. At naphthalene doses of 133 mg/kg/day for 13 weeks, naphthalene had no effect on immune function (Shopp et al. 1984). After 14 days thymus weights were reduced approximately 30% in male mice but no differences were seen with a dose of 133 mg/kg/day at 13 weeks (Shopp et al. 1984). There was lymphoid depletion of the thymus in 2 of 10 female rats exposed to 400 mg/kg/day naphthalene for 13 weeks (Battelle 1980b).

Spleen weights were reduced approximately 20% in female mice exposed to 267 mg/kg/day naphthalene for 14 days and 25% in females exposed to 133 mg/kg/day for 13 weeks (Shopp et al. 1984).

Monocyte concentrations were significantly elevated in male and female mice exposed to 71.6-143.7 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The increase in monocyte counts appeared to be dose related. The authors hypothesized that these changes may have been a physiological response to the pulmonary alveolar proteinosis seen in the exposed animals. There were no changes in spleen or thymus weights and the histopathology of these tissues was normal.

No studies were located that documented immunological or lymphoreticular effects in animals after oral exposure to 2-methylnaphthalene.

The highest NOAEL values and all LOAEL values from each reliable naphthalene study for immunological/lymphoreticular effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. The highest NOAEL value for the single 1-methylnaphthalene study for immunological/lymphoreticular effects is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

The neurologic symptoms of naphthalene ingestion reported in human case studies include confusion (Ojwang et al. 1985), altered sensorium (Gupta et al. 1979), listlessness and lethargy (Bregman 1954; Chusid and Fried 1955; Kurz 1987; MacGregor 1954; Zuelzer and Apt 1949), and vertigo (Gidron and Leurer 1956). Muscle twitching, convulsions (Kurz 1987; Zuelzer and Apt 1949), decreased responses to painful stimuli, and coma occurred prior to death in individuals who ingested naphthalene (Gupta et al. 1979; Kurz 1987). At autopsy, the brain has appeared edematous (Gupta et al. 1979; Kurz 1987), with separation of neural fibers and swelling of myelin sheaths being noted histologically (Gupta et al. 1979). The neurologic symptomatology could result from the cerebral edema, which was probably secondary to acute hemolysis.

No studies were located that documented neurological effects in humans after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

Dose-related clinical signs of neurotoxicity were apparent in female Sprague-Dawley rats exposed to doses of 50, 150, or 450 mg/kg/day naphthalene for 10 days during organogenesis. Slow respiration and lethargy were observed in a large percentage of the exposed animals. Some rats were dazed, had periods of apnea, or were unable to move after exposure. In the lowest dose group, 73% of the animals were affected on the first day of dosing. In the two higher dose groups over 90% of the rats were affected (NTP 1991a).

The animals in the lowest dose group acclimatized quickly. Symptoms were most apparent during the first 2 days of dosing. Signs of neurotoxicity persisted for longer periods in the higher dose groups. The severity and persistence of symptoms were related to dose. These effects were used as the basis of the oral acute MRL for naphthalene (NTP 199la). Comparable neurological effects were not recorded for Fischer-344 rats exposed to doses of up to 400 mg/kg/day for 13 weeks or for mice at doses of up to 200 mg/kg/day (Battelle 1990a, 1990b).

There were no changes in the brain weights in mice exposed to naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the brain were noted in mice at doses of up to 200 mg/kg/day (Battelle 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (Battelle 1980b).

Absolute brain weight was significantly increased in male mice fed diets containing 71.6 or 140.2 mg/kg/day 1-methylnaphthalene for 81 weeks (Murata et al. 1993). The increases in brain weights were not dose related and there were no histopathological abnormalities of the brain. There were no differences in organ weights or histopathology in the female mice given comparable doses.

No studies were located that documented neurological effects in animals after oral exposure to 2-methylnaphthalene.

The highest NOAEL values from each reliable study for neurological effects for naphthalene exposure in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. The highest NOAEL value for the single 1-methylnaphthalene study for neurological effects is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located that documented reproductive effects in humans after oral exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

Oral exposures of pregnant rabbits to naphthalene at dosages up to 400 mg/kg/day (gestational days 6-l8, using methylcellulose as the vehicle, resulted in no apparent adverse reproductive effects (PRI 1986). When administered in corn oil to pregnant mice, however, a dosage of 300 mg/kg/day (gestational days 7-14) resulted in a decrease in the number of live pups per litter (Plasterer et al. 1985). It is not clear whether the observed differences in response are attributable to species differences or a possible increase in the absorption of naphthalene when it is administered in corn oil.

Transient signs of neurotoxicity were present in female rats exposed to doses of 50, 150, or 450 mg/kg/day on gestational days 6-15 (NTP 1991a). Effects on maternal weight gain were noted in the mid- and high-dose groups but not in the lowest dose group. The mid-dose group had a 31% decrease in weight gain while the high-dose group had a 53% weight gain decrease.

No treatment-related effects were reported on testicular weights of mice administered naphthalene at doses up to 267 mg/kg/day for 14 days or 133 mg/kg/day for 90 days (Shopp et al. 1984). No gross or histopathological lesions of the testes were noted in mice at doses of up to 200 mg/kg/day (Battelle 1980a) or in rats at doses of up to 400 mg/kg/day after 13 weeks of exposure (Battelle 1980b).

No studies were located that documented reproductive effects in animals after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

In humans, transplacental exposure of the fetus to naphthalene that had been ingested by the mother resulted in neonatal (and presumably fetal) hemolytic anemia (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). No estimates of dose or duration were available, although in one case

naphthalene consumption was described as being most pronounced during the last trimester (Zinkham and Childs 1958).

No studies were located that documented developmental effects in humans after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

No congenital abnormalities were observed after oral administration of naphthalene at 300 mg/kg/day to pregnant mice on days 7-14 of gestation (Plasterer et al. 1985), or at doses up to 400 mg/kg/day to pregnant rabbits on days 6-18 of gestation (PRI 1986). Similarly, naphthalene was not teratogenic in rats at doses up to 450 mg/kg/day during gestation days 6-15 (NTP 1991a). However, there was a slight, but dose-related, increase in fused sternebrae in female pups of rabbits administered doses of 20-120 mg/kg/day on days 6 through 19 of gestation (NTP 1992b). These effects were seen in 2 of 21 litters at 80 mg/kg/day and 3 of 20 litters at 120 mg/kg/day. No other developmental effects were noted in this study.

No studies were located that documented developmental effects in animals after oral exposure to 1-methylnaphthalene or 2-methylnaphthalene.

The highest NOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located that documented genotoxic effects in humans or animals after oral exposure to naphthalene, l-methylnaphthalene, or 2-methylnaphthalene. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located that documented carcinogenic effects in humans after oral exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

In a 2-year feeding study of rats receiving naphthalene at about 41 mg/kg/day, no tumors were reported (Schmahl 1955). Specific details pertaining to the tissues examined were not provided

Long-term exposure (81 weeks) of mice to 71.6 or 140.2 mg/kg/day 1-methylnaphthalene in the diet was associated with a significant increase in pulmonary adenomas in males but not females (Murata et al. 1993). Adenomas were approximately six times more prevalent in the exposed males than in the controls. The adenomas were located in the bronchial and alveolar region of the lungs.

There were no adenocarcinomas in the lungs of the control and low dose animals, but there were three tumors noted in the high-dose males (140.2 mg/kg/day) and one in the high-dose females (143.7 mg/kg/day) (Murata et al. 1993). The tumors did not appear to be statistically related to compound administration.

No studies were located that documented carcinogenic effects in animals after oral exposure to 2-methylnaphthalene.

2.2.3 Dermal Exposure

2.2.3.1 Death

Two cases of hemolytic anemia were observed in infants exposed to naphthalene-treated diapers (Schafer 1951; Valaes et al. 1963). One case was fatal. Jaundice, methemoglobinemia, hemolysis, and cyanosis were noted. In the fatal case the symptoms persisted, even after the naphthalenecontaining diapers were no longer used (Schafer 1951). The author suggested that use of baby oil on the infant's skin might have facilitated the naphthalene absorption.

No treatment-related deaths occurred within the 14-day observation period when naphthalene was applied at 2,500 mg/kg to the skin of male and female rats or when doses of up to 1,000 mg/kg/day were applied to the skin for 6 hours/day, 5 days/week for 13 weeks (Gaines 1969; Frantz et al. 1986). There were also no deaths in New Zealand White rabbits after application of 2,000 mg/kg naphthalene to intact and abraded shaved areas of skin in an LD_{50} study (Papciak and Mallory 1990).

No studies were located that documented lethal effects in humans or animals after dermal exposure to 1-methylnaphthalene or 2-methylnaphthalene.

2.2.3.2 Systemic Effects

No studies were located that documented musculoskeletal effects in humans or animals after dermal exposure to naphthalene. The highest NOAEL and all LOAEL values for dermal exposure to naphthalene are recorded in Table 2-3. No data for systemic effects in humans or animals from dermal exposure to 1 -methylnaphthalene or 2-methylnaphthlene were located.

Respiratory Effects. No studies were located that documented respiratory effects in humans after dermal exposure to naphthalene.

No histological changes of the lungs were noted in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Cardiovascular Effects. No studies were located that documented cardiovascular effects in humans after dermal exposure to naphthalene.

No differences in organ weight or histological changes of the heart were noted in rats dermally treated with 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Gastrointestinal Effects. No studies were located that documented gastrointestinal effects in humans after dermal exposure to naphthalene.

No histological changes of the esophagus, stomach, or intestines were noted in rats dermally treated with 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Hematological Effects. Hemolytic anemia was reported in infants dermally exposed to diapers or other clothing treated with naphthalene mothballs (Dawson et al. 1958; Schafer 1951; Valaes et al. 1963). Jaundice, fragmentation of erythrocytes, Heinz bodies, methemoglobinemia, and reticulocytosis were observed. Several of the infants had G6PD deficiencies. Individuals with this genetic disorder are particularly susceptible to hemolysis from chemical agents. The application of oil to the skin was

TABLE 2-3. Levels of Significant Exposure to Naphthalene - Dermal

Species/ strain	Exposure/ duration/ frequency/ (specific route)	System	NOAEL (mg/kg)	LOAEL			Reference
				Less serious (mg/kg)		Serious (mg/kg)	
ACUTE EXPOSURE							
Death							
Rabbit New Zealand White	once 24hr contact						Papciak and Mallory 1990
Systemic							
Rabbit New Zealand White	once 24hr contact	Dermal		2000	(skin irritation, edema, fissuring)		Papciak and Mallory 1990
Rabbit	once	Dermal		125	(reversible erythema)		PRI 1985a
Immuno/Lymphor							
Gn pig	3 wk 1x/wk		1000				PRI 1985c
INTERMEDIATE EXPOSURE							
Systemic							
Rat	90 d 5d/wk 6 hr/d	Resp	1000				Frantz et al. 1986
		Cardio	1000				
		Gastro	1000				
		Hemato	1000				
		Hepatic	1000				
		Renal	1000				
		Dermal	300	1000	(increased incidence of excoriated skin and papules)		

Cardio = cardiovascular; d = day(s); Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

assumed to aid the absorption of naphthalene, as shown by the increasing severity of symptoms (jaundice and cyanosis) even after the use of the naphthalene-containing diapers ceased (Schafer 1951).

There were no changes in hemoglobin, hematocrit, red blood cell count, leukocyte count, or platelet count at 4 and 13 weeks in rats treated with doses of up to 1,000 mg/kg/day applied to the skin (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986).

Hepatic Effects. The liver was enlarged in two infants who experienced acute hemolysis after dermal exposure to naphthalene (Dawson et al. 1958; Schafer 1951). The relationship between liver enlargement and potential naphthalene-induced hemolysis is unknown.

There were no differences in liver weights or histological damage to the liver in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986). In addition, the levels of aspartate amino transferase, alanine amino transferase, urea nitrogen, and bilirubin were not elevated in the exposed rats as compared to the controls.

Renal Effects. No studies were located that documented renal effects in humans after dermal exposure to naphthalene.

There were no differences in kidney weights or histological damage to the liver in rats dermally treated with doses of up to 1,000 mg/kg/day naphthalene (6 hours/day, 5 days/week) for 13 weeks (Frantz et al. 1986). In addition, the results of urinalysis conducted at 4 and 13 weeks on the treated rats were not different from the control results, indicating that there was no impairment of kidney function.

Dermal Effects. No studies were located that documented dermal effects in humans after dermal exposure to naphthalene.

A study in rabbits has shown that naphthalene is a mild dermal irritant, causing erythema and fissuring, when directly applied to the shaved, abraded or nonabraded skin under a dressing; healing occurred within 6-7 days (Papciak and Mallory 1990; PRI 1985a). In rats that were dermally treated for 6 hours/day, 5 days per week, for 13 weeks with 1,000 mg/kg/day naphthalene, there was an increased incidence of excoriated skin lesions and papules (Prantz et al. 1986). However, similar

lesions were seen in the controls and lower dose group animals. At the high dose the naphthalene appeared to exacerbate the severity of the lesions. Acute and chronic exposure of animal skin to naphthalene appears to cause dermal irritation.

Ocular Effects. Two case studies were reported in which humans experienced eye irritation and conjunctivitis as a result of naphthalene exposure (van der Hoeve 1906). In one case a worker accidentally got naphthalene powder in his left eye. The exact amount was unknown but described by the worker as large. Despite immediate cleansing of the eye, the subject experienced conjunctivitis and pain shortly after exposure. Symptoms of irritation subsided but then reappeared 6 weeks later. At that time the subject noticed decreased vision in his left eye. When examined by a doctor, the eye had retinal lesions (one fresh and others seemingly older); the entire retina appeared clouded. The subject's vision in his left eye was poorer than that in the right. Five years earlier, vision in both eyes was the same.

In the second case study, an adult male who worked in a storage area where naphthalene was used as a pesticide complained of ocular pain, conjunctivitis, and impaired vision (van der Hoeve 1906). Neither the duration nor the mode of exposure were described. The subject most likely was exposed to naphthalene vapors. When examined by a doctor, the subject was found to have retinal bleeding and the beginning of a cataract.

Dermal and ocular contact with naphthalene vapors accompanied by inhalation may have contributed to the development of multiple lens opacities in 8 of 21 workers involved with a dye manufacturing process that used naphthalene as a raw material (Ghetti and Mariani 1956). Workers, who were employed at the plant for up to 5 years, melted naphthalene in open vats, resulting in high atmospheric vapor concentrations.

Mild ocular irritation was observed in the nonrinsed eyes of rabbits after instillation of naphthalene at 0.1 mg/eye (Papciak and Mallory 1990; PRI 1985b). Observed effects were reversible within 7 days after exposure. When the eyes were rinsed with water immediately after exposure, there were no signs of irritation (Papciak and Mallory 1990). Oral administration of naphthalene in rats resulted in cataract formation beginning at the posterior outer cortex, suggesting that this region is the most sensitive part of the lens (Kojima 1992). The lenses of pigmented Brown-Norway rats had changes, such as water cleft formation, during the first week that 10 mg/kg/day naphthalene was orally

administered every other day (Murano et al. 1993). These rats were more sensitive to cataract formation than albino Sprague-Dawley rats, presumably because they more effectively metabolized naphthalene to the toxic compound naphthoquinone (Murano et al. 1993).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located that documented immunological or lymphoreticular effects in humans after dermal exposure to naphthalene, l-methylnaphthalene, or 2-methylnaphthalene. An enlarged spleen was noted in two human subjects dermally exposed to naphthalene (Dawson et al. 1958; Schafer 1951). However, spleen enlargement is a result of hemolysis rather than a direct effect of naphthalene on the spleen.

In animals, dermal application of pure naphthalene once per week for 3 weeks did not result in delayed hypersensitivity reactions in guinea pigs (Papciak and Mallory 1990; PRI 1985c).

No studies were located that documented immunological or lymphoreticular effects in animals after dermal exposure to 1-methylnaphthalene or 2-methylnaphthalene.

A NOAEL for immunological/lymphoreticular effects following dermal exposure to naphthalene is recorded in Table 2-3.

No studies were located that documented the following health effects in humans or animals after dermal exposure to naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene.

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located that documented carcinogenic effects in humans or animals after dermal exposure to naphthalene, l-methylnaphthalene, or 2-methylnaphthalene.

2.3 TOXICOKINETICS

Little information is available that documented the toxicokinetics of naphthalene in humans by any route of exposure. No information on the toxicokinetics of 1-methylnaphthalene or 2-methylnaphthalene in humans was located. The available animal data pertaining to naphthalene are described in the following sections. The relevance of this information to the toxicokinetics of naphthalene in exposed humans, however, is not known

No toxicokinetic data on 1-methylnaphthalene-exposed animals were located. Animal data pertaining to 2-methylnaphthalene were limited.

2.3.1 Absorption

Based on the presence of adverse effects following exposure, humans and animals can absorb naphthalene by pulmonary, gastrointestinal, and cutaneous routes. However, the rate and extent of naphthalene absorption are unknown in many instances.

2.3.1.1 Inhalation Exposure

Clinical reports suggest that prolonged exposure to naphthalene vapors, can cause adverse health effects in humans (Harden and Baetjer 1978; Valaes et al. 1963; Linick 1983). Unfortunately, the rate and extent of naphthalene absorption were not determined in these studies. Presumably naphthalene moves across the alveolar membrane by passive diffusion through the lipophilic matrix.

No animal data that documented the absorption of naphthalene after inhalation were located. The only data observed in animal studies involved localized effects in the lungs and nasal passages. Thus, it is not possible to conclude that they were the consequence of absorbed naphthalene. However, absorption can be presumed to occur based on the human data.

No information has been located that documented the absorption of 1-methylnaphthalene or 2methylnaphthalene in humans or animals after inhalation exposure. Fogging studies in dogs suggest some absorption of these chemicals through the alveolar membrane.

2.3.1.2 Oral Exposure

Several case reports indicate that naphthalene ingested by humans can be absorbed in quantities sufficient to elicit toxicity (Bregman 1954; Chusid and Fried 1955; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Mackell et al. 1951; Ojwang et al. 1985; Santhanakrishnan et al. 1973; Shannon and Buchanan 1982; Zuelzer and Apt 1949). However, no studies have been located that report the rate or extent of absorption. Absorption of naphthalene presumably occurs by passive diffusion through the lipophilic matrix of the intestinal membrane.

In one patient who died as a result of naphthalene ingestion, 25 mothballs were found in the stomach 5 days after her death (Kurz 1987). A single naphthalene mothball reportedly weighs between 0.5 and 5g depending on its size (Ambre et al. 1986; Siegel and Wason 1986). The gastric contents of a person who mistakenly ingested naphthalene flakes still smelled strongly of naphthalene at least 2 days following ingestion (Ojwang et al. 1985). These findings suggest that dissolved naphthalene is transported slowly into the intestines. Uptake from the intestines is governed by the partition coefficient between the materials in the intestinal lumen and the membrane lipids. Ingestion of mothballs or other forms of particulate naphthalene will lead to continued absorption over a period of several days as the solid dissolves. Unfortunately none of the human data permit a quantitative evaluation of absorption coefficients or rates.

No information that documented the absorption of naphthalene after oral administration to animals has been located. The occurrence of systemic effects in dogs, mice, rats, and rabbits indicates that gastrointestinal absorption does occur. Toxicological evidence also suggests that absorption is facilitated when naphthalene is dissolved in a lipophilic medium such as corn oil (Plasterer et al. 1985).

No information was located that documented the absorption of 1-methylnaphthalene in humans or animals after oral administration. Systemic effects observed after the ingestion of 1-methylnaphthalene demonstrate that intestinal absorption does occur in rats.

No information has been located that documented absorption in humans after oral exposure to 2-methylnaphthalene. Small doses of 2-methylnaphthalene appear to be rapidly absorbed from the gastrointestinal tract in guinea pigs. At least 80% of a 10 mg/kg oral dose of 2-methylnaphthalene was absorbed within 24 hours based on recovery of the radiolabel in the urine (Teshima et al. 1983).

2.3.1.3 Dermal Exposure

Several cases of naphthalene toxicity in neonates have been reported in which the proposed route of exposure was dermal (Dawson et al. 1958; Schafer 1951). Each case involved the use of diapers which had been stored in contact with naphthalene (mothballs or naphthalene flakes). The authors proposed that the naphthalene was absorbed through the skin, causing hemolytic anemia. It was suggested that this absorption may have been enhanced by the presence of oils which had been applied to the babies' skin (Schafer 1951). Inhalation of vapors from the treated diapers probably contributed to the total exposure.

Naphthalene was rapidly absorbed when the neat material was applied for a 48-hour period under a sealed glass cap to shaved patches of rat skin. Half of the sample (3.3 $\mu g/cm^3$) was absorbed in 2.1 hours (Turkall et al. 1994). When the naphthalene was mixed with either a sandy soil or a clay soil prior to contact with the skin, the presence of the soil slowed the absorption (Turkall et al. 1994). The absorption half-time from the clay and sandy soil samples were 2.8 and 4.6 hours, respectively. The rate of absorption did not influence the total amount of naphthalene absorbed in 48 hours since the areas under the plasma concentration curve did not differ significantly with any of the three exposure scenarios (0.42-0.63%/mL hour). The authors proposed that naphthalene was absorbed more slowly from the sandy soil than the clay soil because the sandy soil had a higher organic carbon content (Turkall et al. 1994). The sandy soil contained 4.4% organic matter and the clay soil 1.6% organic matter.

No information was located that documented the absorption of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals after dermal administration.

2.3.2 Distribution

There are limited data concerning the distribution of naphthalene in human tissues. Naphthalene was present in 40% of the adipose tissue samples that were analyzed as part of the National Human Adipose Tissue Survey (Stanley 1986). The maximum concentration observed was 63 ng/g. Naphthalene was also detected in human milk (concentration not reported) (Pellizzari et al. 1982). The source term that accounted for the presence of naphthalene in milk and body fat is not known with certainty. The use of cigarettes or wood-burning fuel sources are two possibilities.

Information is available for the distribution of naphthalene in swine after oral exposure, the distribution of naphthalene in rats after dermal exposure, and the distribution of 2-methylnaphthalene in guinea pigs after oral exposure. No data were located for the inhalation exposure routes and no data were identified on the distribution of l-methylnaphthalene by any route of exposure.

2.3.2.1 Inhalation Exposure

No information has been located that documented the distribution of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene by humans or animals after inhalation exposure.

2.3.2.2 Oral Exposure

Naphthalene can cross the human placenta in concentrations high enough to cause red cell hemolysis and lead to anemia in newborn infants of mothers who consumed naphthalene during pregnancy (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958).

The distribution of naphthalene and its metabolites in young pigs given a single dose of 0.123 mg/kg (4.8 Ci/kg) ^{14}C-labeled naphthalene was monitored at 24 and 72 hours (Eisele 1985). At 24 hours, the highest percentage of the label (3.48 ± 2.16% dose/mg tissue) was in the adipose tissue. The kidneys had the next highest concentration of label (0.96% dose/mg tissue), followed by the liver (0.26 ± 0.06% dose/mg tissue) and lungs (0.16% dose/mg tissue). The heart contained 0.09 ± 0.04% dose/mg tissue and the spleen contained 0.07 ± 0.01% dose/mg tissue. At 72 hours, the amount of label in the fat had fallen to 2.18 ± 1.16% dose/mg tissue, that in the liver to 0.34 ± 0.24% dose/mg tissue, and the kidneys and lungs contained the same concentration (0.26% dose/mg tissue).

Pigs were also given oral doses of 0.006 mg/kg/day (0.22 Ci/kg/day) ^{14}C-labeled naphthalene for 31 days (Eisele 1985). With repeated administration of the radiolabel, the tissue distribution differed considerably from that observed with a single dose of the compound. The highest concentration of label was in the lungs (0.15% dose/mg tissue), followed by the liver and heart (0.11% dose/mg tissue). There was very little label in the fat tissue (0.03% dose/mg tissue). The spleen had 0.09±0.05% dose/mg tissue and the kidney had 0.09% dose/mg tissue.

In one dairy cow, naphthalene distributed to milk with both single and repeated doses of ^{14}C-labeled naphthalene. The label was distributed between the milk and the milk fat (Eisele 1985). When the cow was given naphthalene for a 31-day period, the amount of label found in the milk remained relatively constant throughout the exposure period. The amount in the milk fat was lower for the first 7 days than it was for the remainder of the exposure.

The tissue distribution of 2-methylnaphthalene was measured in guinea pigs 3, 6, 24, and 48 hours after oral administration of tritium-labeled 2-methylnaphthalene (10 mg/kg; 59 μCi/kg) (Teshima et al. 1983). The highest concentration of label was present in the gallbladder with 20.17 ug at 3 hours and 15.72 μg at 6 hours. (All concentrations are expressed in ug equivalents of ^{3}Hg wet tissue.) At 24 hours the value fell to 0.43 μg and at 48 hours, to 0.04 μg. The presence of label in the gallbladder presumably reflects the excretion of hepatic metabolites in the bile. The values for the kidney were 5.64 μg at 3 hours, 7.62 μg at 6 hours, 0.29 μg at 24 hours and 0.09 ug at 48 hours.

Radiolabelled compound was detected in the liver immediately after exposure (Teshima et al. 1983). When converted to units of mass, hepatic concentrations were 1.71 ug at 3 hours and 2.66 μg at 6 hours, falling to 0.18 μg at 24 hours. Lung concentrations were similar to those for blood at all time points. The amount in blood at 3 hours was 0.75 μg and that for the lungs was 0.69 μg; at 6 hours, the blood had a concentration of 0.71 μg and the lung had 0.76 μg. The half-life of 2-methylnaphthalene in the blood was 10.4 hours. The decay of naphthalene in the other tissues examined was described as biphasic.

2.3.2.3 Dermal Exposure

No information was located that documented the distribution of naphthalene, l-methylnaphthalene, or 2-methylnaphthalene in humans after dermal exposure.

In rats, radiolabel from naphthalene distributed to the ileum, duodenum, and kidney (0.01-0.02% of initial dose) when tissues were analyzed 48 hours after naphthalene contact with the skin (Turkall et al. 1994). The largest concentration was found at the site of application (0.56% of initial dose). A total of 20 tissues were evaluated; the percentage of label in all other tissues was minimal.
No information that documented the distribution of 1-methylnaphthalene or 2-methylnaphthalene in dermally exposed animals was located.

2.3.2.4 Other Exposure Routes

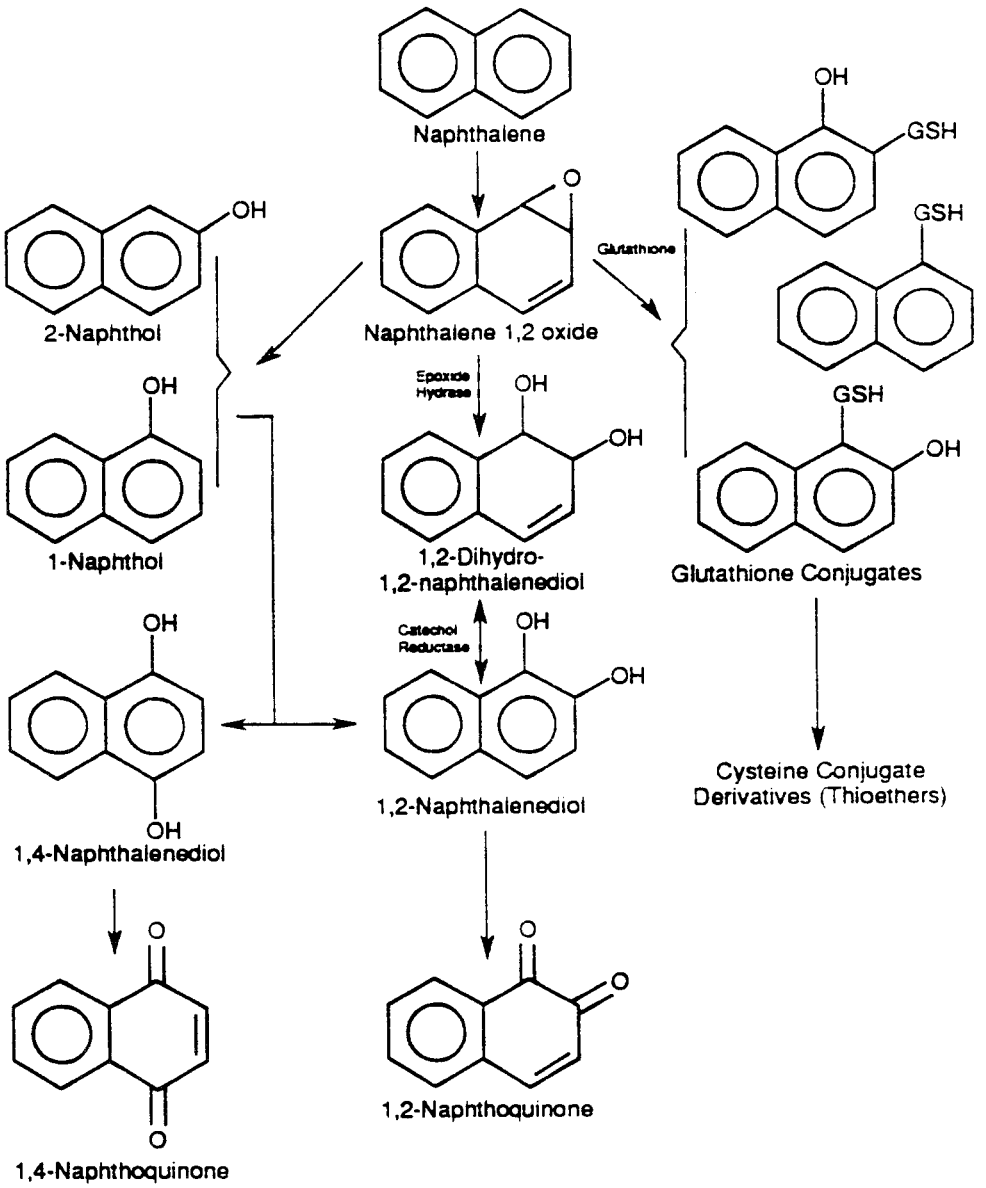
After intraperitoneal administration in mice, ^{14}C-labeled 2-methylnaphthalene distribution was measured in the fat, kidney, liver, and lung for 24 hours (Griffin et al. 1982). The amount of label in the fat peaked 3 hours after exposure and remained higher than the amount of label in other tissues at 8 hours The liver, kidney and lung followed the fat in order of decreasing concentration. The maximum concentration in the fat was 13 nmol equivalentdmg wet weight. The maximum value for the liver was 3.5 nmol equivalents/mg wet weight at 1 hour. Maximum values were about 1.75 nmol equivalents/mg wet weight for the kidneys at 2 hours and 0.8 nmol equivalents/mg wet weight for the lungs at 4 hours.

2.3.3 Metabolism

The metabolism of naphthalene is complex. Up to 21 various metabolites (oxidized derivatives and conjugates) have been identified in the urine of animal species (Homing et al. 1980; Kanekal et al. 1990; Wells et al. 1989). Figure 2-3 illustrates the early steps of naphthalene metabolism. The initial metabolic reaction is the microsomal production of an epoxide intermediate. Many of the derivatives illustrated in Figure 2-3 undergo subsequent oxidation reactions to form trihydroxylated and tetrahydroxylated compounds (Homing et al. 1980). Some metabolites are conjugated with glutathione, glucuronic acid, or sulfate. The glutathione conjugates undergo additional reactions with loss of the glutamyl and glycyl groupings to form a variety of cysteine derivatives (thioethers). There are differences in naphthalene metabolism between tissues and between species.

Little information is available pertaining to the metabolism of naphthalene by humans. Naphthol (isomer not specified) was found in the urine of patients 4 days after naphthalene ingestion; a smaller

FIGURE 2-3. Proposed Pathways for Naphthalene Metabolism



amount was detected 1 day later; and none was found in any specimens collected thereafter (Zuelzer and Apt 1949). In a different study, the urine of an l8 month-old child was found to contain 1-naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone, approximately 9 days after exposure (Mackell et al. 1951). Although the case appeared to involve oral ingestion, the route of exposure could not be established conclusively. With the exception of the 1,4-naphthoquinone, these metabolites were still present on day 13 but not on day 17.

Microsomes isolated from human lung tissue metabolize naphthalene to dihydro-1 ,2-naphthalenediol and three different glutathione adducts (Buckpitt and Richieri 1984; Buckpitt and Bahnson 1986). Among the specimens tested (from two men and one woman, ages 60-77), considerable variability was noted regarding the amounts of each metabolite generated.

Microsomes isolated from six histologically normal human livers produced 1,2-dihydro-1,2-naphthalenediol as the principle stable metabolite and I-naphthol as a minor metabolite (Tingle et al. 1993). The ratio of these two metabolites was 8.6: 1. Production of 1,2-dihydro-1 ,2-naphthalenediol occurred as the result of epoxide hydrolase activity on 1,2-naphthaleneoxide. Several cytochrome P-450 participate in naphthalene epoxidation. Epoxide hydrolase inhibition increases the amount of 1 -naphthol formed by liver microsomes.

The urinary metabolites of naphthalene were evaluated following oral (rats and rabbits) and intraperitoneal (mice, rats, and guinea pigs) administration (Comer and Young 1954). All tested species excreted 1- and 2-naphthol, 1,2-dihydro- 1,2-naphthalenediol, 1 -naphthylsulfate, and with the exception of guinea pigs, 1-naphthylglucuronic acid. A probable, but not clearly confirmed metabolite was a glucuronic acid conjugate of 1,2-naphthalenediol which was also present in all species. 1,2-Dihydro-2-hydroxy- 1 -naphthyl glucuronic acid was found in rats and rabbits, while guinea pigs alone were found to excrete unconjugated 1,2-naphthalenediol.

The glucuronic acid conjugate of dihydronaphthalenediol was also present in the urine of calves (Bakke et al. 1990). A slightly larger portion of the dose was excreted as dihydro-1-hydroxy-2-cysteine derivative. These two metabolites accounted for 81% of the dose. 2-Naphthylsulfate and 2-naphthylglucuronic acid could not be detected in rats, rabbits, and guinea pigs (Comer and Young 1954). There were no differences in the metabolites found after oral and intraperitoneal administrations in the rat (the only species tested by both routes).

Intraperitoneal administration of naphthalene to male rats resulted in the urinary excretion of 80-95% of the administered dose as conjugated metabolites including glucuronides, sulfates, and thioethers (Homing et al. 1980). The major metabolites were identified as 1-naphthol, 2-naphthol, 1,2-naphthalenediol, 1,2-dihydro-1,2-naphthalenediol (cis and trans), 1,4-dihydro- 1,4 naphthalenediol-, (cis and trans) and 1,1-, 2,7-, and 2,6-naphthalenediol. In a similar study, intraperitoneal administration of naphthalene to male mice resulted in urinary excretion of 96% of the administered dose as conjugated metabolites. The major naphthalene metabolites were l-naphthol, trans- 1 -hydroxy-2-methylthio-l ,2-dihydronaphthalene, trans- 1 , 2-dihydro-1,2-naphthalenediol, methyhhionaphthalene, and 2-naphthol. The major sulfur-containing derivative from the seven identified was *N*-acetyl-S-(1-hydroxy-1,2-dihydro-2-naphthenyl) cysteine (Stillwell et al. 1982). The sulfur metabolites are produced by conjugation with glutathione followed by removal of the glycyl and glutamyl moieties and modification of the cysteine. The metabolites identified in both of these studies support the hypothesis that epoxide intermediates play a key role in the metabolism of naphthalene.

A dose-dependent increase in urinary mercapturic acid excretion was observed following gavage doses of naphthalene to rats (Summer et al. 1979). No corresponding increase in thioether excretion was seen in chimpanzees. On the basis of data from 2 animals, glucuronic acid and sulfate conjugates account for the bulk of the conjugated naphthalene in chimpanzees (Summer et al. 1979). Rhesus monkeys also did not demonstrate any increase in urinary excretion of thioethers or depletion of hepatic glutathione following oral doses of up to 200 mg/kg/day (Rozman et al. 1982).

Evidence that intestinal microflora are involved in the production of 1,2-dihydro-1–hydroxymethyl-thionaphthalene glucuronide, naphthols, and naphthol conjugates from premercapturic acid was demonstrated in a study in which radiolabeled naphthalene was administered to bile-cannulated, noncannulated, and germ-free rats. Urinary naphthols, naphthol glucuronides, and methylthioglucuronides were identified in control rats. Bile and urine from cannulated rats and urine from germ-free rats contained no labeled methylthioglucuronide metabolite and only trace amounts of labeled naphthols and naphthol glucuronide conjugates (Bakke et al. 1985). The 1,2-dihydro-1-hydroxy-2-S-(*N*-acetyl) cysteinyl naphthalene conjugate was excreted in urine as 14.4% of the administered dose in bile-cannulated rats within 24 hours and 89% of the dose in germ-free rats. Noncannulated rats excreted 38.1% of the dose in urine as this *N*-acetyl cysteinyl conjugate.

The methyl substituent of 1-methylnaphthalene and 2-methylnaphthalene presents the opportunity for side chain oxidation reactions in addition to the ring oxidation. In rats administered subcutaneous injections of 2-methylnaphthalene, 2-naphthoic acid and naphthoic acid conjugates were identified in the urine (Melancon et al. 1982). The naphthoic acid and various conjugates of the acid were estimated to account for 36-43% of the urinary metabolites. Most (30-35%) of this was found as a glycine conjugate. The urine contained 3-5% unreacted 2-methylnaphthalene; free dihydrodiols accounted for 6-8% of the label. Unidentified highly polar metabolites comprised another 36-45% of the excreted label. At least three diol derivatives of 2-methylnaphthalene were produced by hepatic microsomes from mice (Griffin et al. 1982) suggesting that the ring oxidation reactions of 2-methylnaphthalene are similar to those for naphthalene. Rat liver microsomes also produced 2-hydroxymethylnaphthalene and three diols from 2-methylnaphthalene (Breger et al. 1981, 1983; Melancon et al. 1985). The three diols were identified as 3,4-dihydrodiol, 5,6-dihydrodiol, and 7,8-dihydrodiol (Breger et al. 1983).

Metabolites isolated in the urine of guinea pigs after oral dosing with tritium labeled 2-methylnaphthalene were 2-naphthoic acid and its glycine and glucuronic acid conjugates (Teshima et al. 1983). These metabolites accounted for 76% of the urinary label. Glucuronic acid and sulfate conjugates of 7-methyl- 1-naphthol along with S-(7-methyl-l -naphthyl)cysteine were 18% of the excreted label. No diol metabolites were identified.

No information was located that documented the metabolism of 1-methylnaphthalene. It may be similar to that for 2-methylnaphthalene with oxidation of the side chain and the ring.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Little information is available pertaining to the excretion of naphthalene in humans after inhalation exposure to naphthalene. Workers employed in the distillation of naphthalene oil and at a coke plant had peak levels of urinary 1-naphthol 1 hour after finishing a shift. Of three workers and a nonoccupationally exposed group, naphthalene oil distribution plant workers had the highest concentrations of urinary 1-naphthol, with a mean excretion rate of 0.57% mg/hour. Investigators calculated the half-life for the urinary excretion of 1-naphthol as approximately 4 hours (Bieniek

1994). This urinary metabolite may indicate both exposure to naphthalene and low concentrations of 1-naphthol during naphthalene oil distillation (Bieniek 1994). No studies were located that documented excretion in humans after inhalation exposure to 1-methylnaphthalene, or 2-methylnaphthalene.

No studies were located that documented excretion in animals after inhalation exposure to naphthalene, 1 -methylnaphthalene, or 2-methylnaphthalene.

2.3.4.2 Oral Exposure

Little information is available pertaining to the excretion of orally ingested naphthalene by humans. The urine of one patient was tested for naphthalene and its derivatives. Naphthol was found at the time of hospital admission (4 days post-ingestion). Smaller quantities were present 1 day later, but naphthalene was not detected in later specimens (Zuelzer and Apt 1949). In another instance, the urine of an 18-month-old child was found to contain 1-naphthol, 2-naphthol, 1,2-naphthoquinone, and 1,4-naphthoquinone (but no naphthalene) 9 days after exposure (Mackell et al. 1951). With the exception of the l,4-naphthoquinone, these metabolites were still detectable on day 13, but not on day 17. These data indicate that urinary excretion of metabolites may be prolonged following exposure. It is important to note, however, that delayed dissolution and absorption from the gastrointestinal tract may also be a contributing factor. Unabsorbed naphthalene was visible in the fecal matter after ingestion of naphthalene flakes or mothballs in several individuals (Zuelzer and Apt 1949).

In nonhuman primate studies, Rhesus monkeys given naphthalene at oral doses up to 200 mg/kg did not excrete naphthalene as thioethers in urine or feces (Rozman et al. 1982). In a similar study, chimpanzees orally administered naphthalene at 200 mg/kg did not excrete naphthalene as thioethers in urine (Summer et al. 1979). These data suggest that glutathione conjugation of naphthalene may not occur to any great extent in nonhuman primates. Data from two chimpanzees indicate that most of the naphthalene excreted in this species is excreted as glucuronic acid and sulfate conjugates (Summer et al. 1979).

In rats administered radiolabeled naphthalene, the amount of label recovered in 24 hours was 77-93% in urine and 6-7% in feces (Bakke et al. 1985). There was a dose-dependent increase in urinary

thioether excretion following gavage doses of naphthalene at 30, 75, and 200 mg/kg within 24 hours (Summer et al, 1979). The levels of thioethers excreted accounted for approximately 39, 32, and 26% of the three dose levels tested.

No information was located that documented excretion in humans after oral exposure to 2-methylnaphthalene. In guinea pigs, 80% of a 10 mg/kg tritium-labeled dose was excreted in the urine within 24 hours and about 10% was recovered in the feces (Teshima et al. 1983). Most of the excreted material (76%) was found as 2-naphthoic acid or its conjugates. About 18% of the recovered label was found as conjugates of 7-methyl-1-naphthol.

No studies were located that documented excretion in humans or animals after oral exposure to 1 -methylnaphthalene.

2.3.4.3 Dermal Exposure

No reports have been located which discuss the excretion of naphthalene, l-methylnaphthalene, or 2-methylnaphthalene in humans following dermal exposure.

The dermal exposure of rats to radiolabeled naphthalene was evaluated over a 48-hour period (Turkall et al. 1994). Naphthalene samples were applied to shaved areas on the skin under a sealed plastic cap. Neat naphthalene or naphthalene adsorbed to the surface of sandy soil or clay soil was tested. In all three cases, excretion of the label was primarily through the urine (70-87%). With the pure naphthalene and naphthalene adsorbed to clay soil, the exhaled air accounted for 614% of the administered label. Exhaled air contained only 0.9% of the label in the sandy soil group. This finding was presumably related to the slower adsorption of naphthalene from the sandy soil and its more rapid metabolism to nonvolatile metabolites. Less than 0.02% of the label was exhaled as carbon dioxide in all groups. The feces contained 24% of the label.

The primary metabolites in the urine after dermal application of naphthalene were 2,7-dihydroxynaphthalene, 1,2-dihydroxynapththalene, and 1,2-naphthoquinone (Turkall et al. 1994). The ratio of these metabolites for pure naphthalene and naphthalene adsorbed to clay soil were roughly 3:2:1. For the sandy soil, the corresponding ratio was 3:2:1.5. Small amounts of 1-naphthol and

2-naphthol were also excreted. In all cases, the amount of urinary free naphthalene was less than 0.4% of the administered label.

No studies were located that documented excretion in animals after dermal exposure to 1-methylnaphthalene or 2-methylnaphthalene.

2.3.4.4 Other Exposure Routes

In mouse studies using the intraperitoneal or subcutaneous exposure routes, several naphthalene metabolites were excreted in the urine. After intraperitoneal administration of naphthalene, conjugates accounted for 80-95% of the urinary metabolites (Horning et al. 1980; Stillwell et al. 1982). Much of the conjugated material was present as thioethers (glutathione conjugates and their derivatives). The major oxidation products of naphthalene metabolism were 1 -naphthol and trans- 1,2-dihydro-1 ,2-naphthalenediol.

Following subcutaneous administration of 0.3 mg/kg ^{14}C-labeled 2-methylnaphthalene, 55% was found in the urine of rats (Melancon et al. 1982). Naphthoic acid and its glycine conjugate were identified. Three other metabolites were tentatively identified as isomeric diols.

2.3.5 Mechanisms of Action

Detailed information on the mechanism of toxicity is available for three of the health effects associated with naphthalene exposure: hemolysis, the development of lens opacities (cataracts), and pulmonary toxicity. These mechanisms are discussed below. Some information is also available that documented the pulmonary effects of 1-methylnaphthalene and 2-methylnaphthalene.

Hemolysis. Humans experience red-cell hemolysis after naphthalene exposure by the inhalation, oral, and dermal routes. In general, animal species are less susceptible than humans. There are no reports of naphthalene-induced hemolysis in either rats or mice; however, hemolysis has been observed in dogs.

Chemically induced red blood cell hemolysis is caused by a breakdown of the system that protects the erythrocyte biomolecules from oxidation. In the erythrocyte, glutathione peroxidase rather than

catalase is the major antioxidant enzyme. Glutathione peroxidase (Gpx) is a selenium containing metalloprotein that utilizes reduced glutathione as a cofactor. Oxidized glutathione is reduced by glutathione reductase, a nicotinamide adenine dinucleotide phosphate (NADPH)-requiring enzyme.

The primary source of erythrocyte NADPH is glucose-6-phosphate oxidation by the enzyme G6PD. Individuals who suffer from a genetic defect resulting in a modified enzyme structure (a recessive trait) have a reduced capacity to produce NADPH. Accordingly, they are more susceptible to red cell hemolysis than individuals without this defect (Gosselin et al. 1984). There is some evidence that heterozygotes may also have an increased susceptibility to red cell hemolysis (Dawson et al. 1958).

When the red blood cell is exposed to oxidizing agents, heme iron is oxidized to the ferric state, producing methemoglobin. This in turn leads to Heinz body formation. It is believed that free radical oxygen modifies membrane lipids leading to increased membrane fragility and lysis. Destruction of the red blood cells decreases erythrocyte counts and stimulates hematopoiesis (leading to increased numbers of reticulocytes). The oxygen carrying capacity of the blood is reduced. Cell lysis releases heme and protein into the blood. Heme breakdown produces bilirubin and biliverdin, causing jaundice. Both erythrocytes and heme breakdown products (urobilinogen) spill into the urine.

Several suggestions can be made regarding the impact of naphthalene on this sequence of events. Since naphthalene is conjugated with glutathione for excretion, it can reduce the supplies of glutathione available for glutathione peroxidase and increase the vulnerability of the cell to oxidation. It is also possible that a naphthalene metabolite may act as an inhibitor for either glutathione peroxidase or glutathione reductase. Glutathione reductase activity was reduced in children who experienced hemolysis following dermal exposure to naphthalene and in related family members (Dawson et al. 1958). Both glutathione peroxidase and glutathione reductase activity were decreased in the lens of rats orally exposed to naphthalene (Rathbun et al. 1990; Tao et al. 1991).

Each of the hypotheses discussed above would serve to increase the sensitivity of any naphthalene-exposed subject to an external oxidizing agent. However, given the severity of the hemolysis that follows naphthalene exposure, it is probable that naphthalene or a naphthalene metabolite also acts as an oxidizing agent in the erythrocyte. Unfortunately, data could not be identified which would correlate the production of any particular metabolite with initiation of red cell peroxidation.

Cataracts. Although there are reports that inhalation, oral, and dermal naphthalene exposure in humans can lead to lens opacities (Grant 1986), the case studies or industrial exposure reports that link naphthalene to cataracts in humans have not been verified by well-conducted epidemiological studies of individuals exposed to naphthalene vapors on a chronic basis. In addition, impurities present in the naphthalene may have contributed to the cataract development in all recorded human cases. Conversely, there are data from a number of well-conducted studies which demonstrate that naphthalene can induce cataracts in animals.

Much of the animal data regarding ocular effects suggest that the toxicity of naphthalene is mediated by the in situ formation of 1,2-naphthalenediol in the lens. It is proposed that metabolism of naphthalene starts in the liver, yielding epoxide metabolites that are subsequently converted to stable hydroxy compounds that circulate to the lens (Van Heyningen and Pirie 1967). The 1 ,2-naphthalenediol metabolite is subsequently oxidized to 1 ,2-naphthaquinone and hydrogen peroxide. The quinone metabolite binds to constituents of the lens (protein, amino acids, and glutathione), disrupting its integrity and transparency (Rees and Pirie 1967; Uyama et al. 1955; Van Heyningen 1976, 1979; Van Heyningen and Pirie 1967; Wells et al. 1989).

Intraperitoneal administration of naphthalene (125-1,000 mg/kg), 1-naphthol (56-562 mg/kg), 1,2-naphthoquinone (5-250 mg/kg) and 1,4-naphthoquinone (5-250 mg/kg) caused a dose-related increase in cataracts in C57BL/6 mice, but administration of 2-naphthol (56-456 mg/kg) did not (Wells et al. 1989). The cataractogenic potency of the naphthoquinones was about ten times that of naphthalene. The cataractogenic potency of 1-naphthol was intermediate to that of naphthalene and the naphthoquinones. The potency of naphthalene was increased by pretreatment with cytochrome P-450 inducers and a glutathione-depleting agent. It was inhibited by pretreatment with a cytochrome P-450 inhibitor. This suggests that the unconjugated oxidized naphthoquinone metabolites are a necessary prerequisite for cataract formation. There are differences in species and strain susceptibility to cataract formation that theoretically relate to the animals' ability to form these metabolites. Naphthalene, 1 -naphthol, 1 ,2-naphthoquinone, and 1,4-naphthoquinone did not form cataracts in DBA/2 mice suggesting the difference between strains is not simply due to metabolite exposure (Wells et al. 1989).

Because hydrogen peroxide is also formed following the oxidation of 1,2-dihyroxynaphthalene, peroxides may play a role in naphthalene-induced ocular damage. Increased levels of ocular lipid

peroxides were noted in rats given incremental doses of naphthalene which increased from 100 to 750 mg/kg/day during a 9 week period (Germansky and Jamall 1988). The antioxidants caffeic acid (527 mg/kg) and vitamin E (250 mg/kg), which have free radical protection properties, and the free radical spin trapping agent α-phenyl-N-t-butylnitrone (PBN) (518 mg/kg) diminished the incidence of cataracts in animals given 750 mg/kg naphthalene (Wells et al. 1989). There were no cataracts in the rats given only PBN.

Support for this mechanism of cataract formation was provided by a gavage study in which 5 rat strains (pigmented and albino) were given 500 mg/kg/day naphthalene for 3 days and 1,000 mg/kg/day for the remainder of the 28-day treatment period (Xu et al. 1992b). After 3 weeks, there was a decrease in reduced glutathione (GSH) in the lens, an increase in protein-glutathione mixed disulfides and an increase in high molecular weight insoluble proteins (Xu et al. 1992a, 1992b). The only metabolite detected in the aqueous humor of the lens was 1,2-dihydro-1,2-naphthalenediol. The authors hypothesized that 1,2-dihydro-1,2-naphthalenediol was oxidized to 1,2-naphthalenediol and then to 1,2-naphthoquinone. The 1,2-naphthoquinone is believed to be responsible for the chemical changes in the eyes either through crosslinking reactions or by generating free radicals (Xu et al. 1992a). All the rats developed cataracts.

The complete mechanism for this sequence of reactions is not clear. In in vitro studies of cataract formation, 1 ,2-dihydro- 1,2,naphthalenediol was the only metabolite that resulted in cataracts that were morphologically the same as those generated in viva (Xu et al. 1992a). Although 1,2-naphthalenediol and naphthoquinone also formed cataracts in lens culture studies, the opacities were located in the outer layer of the cortex rather than inside the lens. Also, the permeability of the cultured lens to the metabolites in the media may have contributed to the differences in lesion location.

When the aldose reductase inhibitor AL01576 was given to rats along with the same naphthalene doses, no cataracts developed (Xu et al. 1992a, 1992b). Aldose reductase is an enzyme found in the lens, liver, and peripheral neurons that reduces aldehyde sugars such as glucose to their corresponding alcohols (McGilvery 1983). It is believed to oxidize 1,2-naphthalenediol to 1 ,2-naphthoquinone; therefore when this reaction is inhibited, the quinone hypothetically does not form and there is no eye damage (Xu et al. 1992a).

Pulmonary Toxicity. There are no reports of pulmonary damage in humans exposed to naphthalene by any exposure route. Overt pulmonary lesions are seen in animal studies using the inhalation route of exposure (NTP 1992a) but not the oral route. However, data from a number of studies indicate that changes in the bronchial epithelium will occur following intraperitoneal exposure to naphthalene when the metabolites responsible for these changes are present in the lungs at a high enough concentration.

Acute exposure to naphthalene by intraperitoneal injection can cause damage to pulmonary bronchiolar epithelial cells, primarily nonciliated Clara cells (Chichester et al. 1994; Honda et al. 1990; Mahvi et al. 1976; O'Brien et al. 1989; O'Brien et al. 1985; Tong et al. 1982; Warren et al. I982). Existing data suggest that stereospecific cytochrome P-450 monooxygenase-dependent metabolic activation of naphthalene to form the reactive intermediate (1R, 2S naphthalene oxide) is a major factor in pulmonary toxicity (Buckpitt and Franklin 1989; Chichester et al. 1994; Warren et al. 1982). The toxicity is thought to be due to the subsequent binding of metabolites in the lung. For the most part, the toxicity is thought to be due to metabolic processes localized within the lungs; however, some data suggest that circulating reactive intermediates from nontarget tissues (particularly the liver) may also be a factor in the cytotoxic injury to the lungs (Kanekal et al. 1990; O'Brien et al. 1989; Warren et al. 1982).

The severity of pulmonary damage and the areas of the lung that are most affected by the naphthalene parallel the distribution of unspecified cytochrome P-450 isozymes in the tracheobronchial tree (Plopper et al. 1992a, 1992b). Mice are the most sensitive to the pulmonary toxicity of naphthalene, followed by hamsters and rats. In mice, the major damage to the Clara cells occurred in the terminal bronchioles, whereas in hamsters, there were greater changes in the proximal airways than in the distal airways. Rats were nearly resistant to any damage of the Clara cells by naphthalene. Intraperitoneal naphthalene also induced hyperplasia in mouse bronchial ciliated cells, a purported nontarget population. The mouse response was characterized by bronchiolar epithelial thickening at low doses and Clara cell cytotoxicity at high doses (Plopper et al. 1994b).

In perfused mouse lungs, the number of Clara cells in the terminal bronchioles decreased from 63% to 30% with 4-hour exposure to 0.13 mg of naphthalene (Kanekal et al. 1990). Clara cells exfoliated and entered the lumen of the airway. Nonciliated Clara cells are more sensitive to damage from naphthalene and other oxidizing agents than ciliated cells of the pulmonary epithelium because of their high concentration of microsomal mixed function oxidases.

Investigators have reported similar effects of naphthalene and naphthalene oxide on cell viability in Clara cell cultures (Chichester et al. 1994). Exposure of cell cultures to 1.3 or 6.5 mg/L naphthalene had no significant effects on cell viability when the cultures were monitored at 120 and 340 minutes after the start of exposure. However, exposure to 64 mg/L and 128 mg/L naphthalene decreased viability by 39% and 88%, respectively. The effect of 72 mg/L (0.5 mM) naphthalene oxide was roughly equivalent to that of an equimolar amount of naphthalene.

Glutathione and glutathione transferase decreased naphthalene-induced Clara cell damage (Chichester et al. 1994). Hypothetically, limited available glutathione leads to changes in the ratios of naphthalene intermediary metabolites, resulting in increased production of the more toxic species. One of the most cytotoxic naphthalene metabolites in the lungs is 1,4-naphthaquinone (Chichester et al. 1994); 1,2-naphthaquinone is toxic to a lesser extent. Naphthalene oxide had a greater effect on Clara cell viability than either 1,2-dihydro- 1,2-naphthalenediol or 1-naphthol.

Clara cell death is postulated to result from interactions between an active naphthalene metabolite and important cell proteins or nucleic acids (O'Brien et al. 1989). When isolated Clara cells were exposed to tritium-labeled naphthalene, naphthalene metabolites were bound selectively to three protein fractions with molecular weights of 15, 30, and 45 kilodaltons (KD). The 15KD protein was the major labeled species (Cho et al. 1994a). The labeled proteins are potentially secretory proteins based on the fact that most of the label could be isolated from the medium rather than the cells (Cho et al. 1994a).

Chronic oral exposure to naphthalene does not have the same effect on lung epithelial exfoliation as acute exposure. This appears to be the result of decreased production of the active metabolite lR,2S naphthalene oxide in cells that have adapted to naphthalene exposure. When mice were given intraperitoneal injections of 200 mg/kg (but not 50 or 100 mg/kg naphthalene) for 7 days and then given a 300-mg/kg challenge, there was no change in the bronchial epithelium (O'Brien et al. 1989). The 300-mg/kg challenge, when given without pretreatment, caused epithelial exfoliation. As the time between the last pretreatment dose and the challenge dose increased from 24 to 144 hours, sensitivity to the challenge increased.

Chronic exposure to 1-methylnaphthalene was associated with the development of alveolar proteinosis (pulmonary damage) in mice given doses of 71.6-143.7 mg/kg/day (Murata et al. 1993). Alveolar

proteinosis is a disorder in which nodules of amorphous protein and lipid form in the distal alveoli, reducing the surface area available for oxygen transport. Symptoms of this disorder include shortness of breath, weakness, cough, and chest pains (Robbins 1976). Pulmonary alveolar proteinosis can be fatal to a minority of affected individuals, especially infants. Most affected patients, however, recover without any biochemical or histological evidence of damage. The etiology of this disease is unknown.

There was no intermediate sacrifice of animals in the study by Murata et al. (1993), so the progression of the proteinosis was not evaluated. However, its occurrence is consistent with data from intraperitoneal studies which illustrate vacuolation, ultrastructural cellular changes, and exfoliation of Clara cells in the bronchioles of mice treated with single doses of 71-426 mg/kg 1-methylnaphthalene (Rasmussen et al. 1986).

Clara cells are nonciliated secretory cells in the lungs that are rich in mixed function oxidase enzymes (O'Brien et al. 1989). Possibly, protein deposits in the proteinosis nodules are the product of reactions between oxidized 1-methylnaphthalene intermediates and surfactant proteins which interfere with normal post-translational modification and maturation of the pulmonary proteins, decreasing their solubility and causing the deposits noted in the proteinosis. The location of the nodules in the distal air passages is consistent with the distribution of Clara cell cytochrome P-450 isozymes in the mouse tracheobronchial tree (Plotter et al. 1992).

No inhalation, oral, or dermal studies of 2-methylnaphthalene were located. However, when administered by the intraperitoneal route, 2-methylnaphthalene had a fourfold greater effect on Clara cell exfoliation than 1-methylnaphthalene did (Rasmussen et al. 1986). Inducers and inhibitors of mixed function oxidase enzymes had little influence on Clara cell damage by 2-methylnaphthalene, but there was a direct correlation between the degree of metabolite binding in the cell and the amount of damage observed (Griffith et al. 1982; Warren et al. 1982). Accordingly, long-term exposure to 2-methylnaphthalene may result in a detectable change in lung tissue.

2.4 RELEVANCE TO PUBLIC HEALTH

Naphthalene gains access to the environment when it is used as a larvicide for moths, as a result of its presence in fossil fuels, and when it is produced during the combustion of wood, tobacco, and other organic materials. The methylated naphthalenes are also found in petroleum products, coal tar, and

tobacco smoke. Industrial discharges contribute to the anthropogenic presence of naphthalene, 1 -methylnaphthalene, and 2-methylnaphthalene in the environment. Data were insufficient to adequately quantitate the relative contribution from each source.

The primary human health concerns associated with naphthalene relate to its hemolytic effects, particularly in individuals who are genetically sensitive as a result of an inherited defect in red blood cell G6PD. Hemolysis has been reported in humans following exposure to naphthalene by the inhalation, oral, and dermal routes.

There are a limited number of instances where naphthalene has been associated with the development of lens opacities in humans. Since a change in lens clarity is an unusual occurrence among those occupationally exposed to naphthalene, impurities may have played a role in the development of lens opacities in the few case studies that have been published.

Studies in animals identify the eyes and lungs as the primary targets of naphthalene toxicity. Following inhalation exposure, naphthalene also causes inflammation and metaplasia of the nasal epithelium in animals.

There is variability in the manifestations and degree of toxicity between animal species. Hemolysis occurs in dogs but not in rodents. Mice are more sensitive than rats to the pulmonary effects of naphthalene, and rabbits are particularly sensitive to its cataractogenic effects. Differences in species sensitivity may relate to differences in the production of the metabolites responsible for the toxic effect. Naphthalene metabolism is complex and leads to the formation of an assortment of hydroxylated derivatives, quinones, and conjugates of glucuronic acid, glutathione, and sulfate. The availability of glutathione for conjugation appears to have a strong influence on the rates of metabolite production in selected tissues.

There were no studies in humans that documented reproductive or developmental effects of naphthalene. In animals, the compound did not adversely affect development in rats or rabbits although in vitro data indicate that some naphthalene metabolites can be embryotoxic.

The results from most short-term tests of mutagenic potential indicate that neither naphthalene nor its metabolites are mutagens, although exposure to naphthalene did result in chromosomal aberrations and

increased sister chromatid exchange incidence in assays using Chinese hamster cell cultures. Studies in mice suggest that naphthalene may increase the risk of lung tumors in humans.

The difference between the health effects of naphthalene in humans and animals and the lack of human dose-response data make it difficult to evaluate the risk for populations living near hazardous waste sites or occupationally exposed to naphthalene. Individuals with the G6PD trait seem to be most at risk from the presence of naphthalene in the environment.

Only two animal studies were located that documented the health effects associated with inhalation, oral, or dermal exposure to l-methylnaphthalene. Only one study involving these exposure routes was located for 2-methylnaphthalene. The number of reticulocytes increased in splenectomized dogs after inhalation exposure to 1-methylnaphthalene, and oral exposure was associated with the development of pulmonary adenomas and alveolar proteinosis in mice. The physiological significance of these findings is uncertain. There were no apparent effects in dogs after inhalation exposure to 2-methylnaphthalene. Both 1-methylnaphthalene and 2-methylnaphthalene are mildly toxic when administered to animals via intraperitoneal injection. However, there is not enough information to assess the risk to public health from exposure to the methylnaphthalenes at hazardous waste sites.

Minimal Risk Levels for Naphthalene

Inhalation MRLs

- An MRL of 0.002 ppm has been derived for chronic inhalation exposure to naphthalene.

  This MRL was derived from a chronic (2-year) inhalation study in mice using exposures of 0, 10, or 30 ppm (NTP 1992a). Groups of mice were exposed for 5 days per week and 6 hours per day. Body weights, clinical signs, and mortality were monitored daily. Hematological measurements were made at 14 weeks, but not thereafter; ophthalmic examinations were performed at 6-month intervals. At sacrifice, gross necropsy of all animals was performed. Histological examination of the tissues was conducted for both the control and high dose animals. Tumor incidence was evaluated in all organs.

This study identified a LOAEL of 10 ppm. A dose-related incidence of chronic inflammation of the epithelium of the nasal passages and lungs was observed. There was metaplasia of the olfactory epithelium and hyperplasia of the respiratory epithelium, but there were no treatment-related gross or histopathological lesions of the organs examined. The data suggest that the observed responses represented a respiratory inflammation and regeneration mechanism. There was an increased incidence of combined alveolar/bronchiolar adenomas and carcinomas in the lungs of the females at the high dose.

The LOAEL of 10 ppm was used for the derivation of the MRL. This concentration was normalized by adjusting for the 6-hour-per-day and 5-day-per-week exposure pattern. An uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) was applied to obtain the MRL. MRL derivation using the Human Equivalent Concentration (HEC) methodology (EPA 1989) could not be conducted because naphthalene is neither reactive nor soluble, and therefore does not fulfill the criteria necessary for HEC determination in a respiratory contaminant (EPA 1990b).

The results of the NTP (1992a) study do not suggest adverse hematological effects in exposed mice. Given that hemolytic anemia is a concern in naphthalene-exposed humans and dogs, the current findings suggest that the MRL may not have been derived in the most sensitive species, or for the most sensitive end point. Furthermore, findings of enhanced bronchiolar sensitivity in mice suggest that their response to respiratory toxins may not be representative of the response for other species.

No appropriate data were located on effects of acute- and intermediate-duration inhalation exposure in humans or animals that could be used to derive acute and intermediate MRLs for inhalation exposure.

Oral MRLs

- An MRL of 0.05 mg/kg/day has been derived for acute oral exposure to naphthalene.

  The MRL was derived from a study of the effects of naphthalene in gravid Sprague-Dawley Rats (NTP 1991a). The animals were administered 0, 50, 150, or 450 mg/kg/day

naphthalene by gavage in corn oil on days 6-15 of gestation. Clinical signs and body weight were monitored daily. The dams were sacrificed on gestation day 20.

The study identified a LOAEL of 50 mg/kg/day for clinical signs of neurotoxicity in the dams. Slow respiration and lethargy were observed in 65-69% of the dams in this dose group. Other signs of neurotoxic effects were periods of apnea, or the inability to breathe after exposure. The rats adjusted to exposure and symptoms diminished with time; they were most pronounced during the first 2 days of dosing. The severity and persistence of symptoms were related to dose.

The MRL was calculated from the LOAEL using an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

- An MRL of 0.02 mg/kg/day has been derived for intermediate oral exposure to naphthalene.

The MRL was derived from a subchronic study in CD-l mice where minimal hepatic effects were observed in females administered 5.3 mg/kg/day (Shopp et al. 1984). Both the males and females were given 0, 5.3, 53, or 133 mg/kg/day naphthalene in corn oil by gavage for 90 days. Following exposure, body weight, clinical signs, and mortality were monitored. Hematological, clinical chemistry, and immunological parameters were evaluated. Gross necropsy was performed, but histological examinations were not conducted.

BUN values were significantly decreased as compared to the controls in the females at all doses. BUN, but not the BUN/creatinine ratio, followed a dose-response relationship. However, the BUNkreatinine ratio for all the exposed females was about 33% lower than the ratio for both the concurrent and the vehicle controls. The BUN/creatinine ratio was lower than that for the controls and vehicle controls in males receiving 53 or 133 mg/kg/day. These results suggest that naphthalene could have inhibited protein catabolism and/or nitrogen metabolism through the urea cycle. A decrease in benzo(a)pyrene hydroxylase activity at all doses in males and in females for the 53 and 133 mg/kg/day doses also suggests minor effects of naphthalene on liver function.

The MRL was calculated from the LOAEL (5.3 mg/kg/day) in males and females using an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to

humans, and 10 for human variability). The corresponding adverse effects were decreased benzo(a)pyrene hydroxylase activity in males and decreased BUN in females

- An MRL of 0.07 mg/kg/day has been derived for chronic oral exposure to l-methylnaphthalene.

  The MRL for 1-methylnaphthalene was derived from an 8l-week study in groups of 50 male and 50 female mice using diets containing 0, 71.6 (males), 75.1 (females), 140.2 (males), or 143.7 (females) mg/kg/day (Murata et al. 1993). Food intake, clinical signs, and body weight were determined throughout the study. At the end of 81 weeks, peripheral blood samples were collected and the animals were sacrificed. Organ weights were determined and the tissues examined histologically; tumors were identified and characterized. Hematological parameters and biochemical indices were evaluated in the blood samples.

Effects were noted in all exposed animals. Most notable was a significantly increased incidence of nodular alveolar proteinosis in males and females. In males, there was also a significant increase in pulmonary adenomas. These changes did not show a dose-response relationship. The alveolar nodules were filled with an amorphous acidophilic material, cholesterol crystals, and foamy cells. They were not accompanied by inflammation, edema, or fibrosis. The LOAEL of 71.6 mg/kg/day for 1-methylnaphthalene in female mice was used for the derivation of the MRL, employing an uncertainty factor of 1,000. The uncertainty factor consists of factors of 10 each for extrapolation from a LOAEL to a NOAEL, interspecies extrapolation, and the protection of sensitive subgroups.

The exposed females in the Murata et al. (1993) study had slight increases in hemoglobin concentrations, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentrations. Both sexes of l-methylnaphthalene-treated mice also had elevated monocyte counts. These findings may have some relevance to findings of anemia in humans exposed to naphthalenecontaining mothballs (Linick 1983; Valaes et al. 1963).

Because the MRL is based on a dietary study, it has considerable relevance for NPL sites involving 1-methylnaphthalene in soil. The results of this single study are not adequate for a direct comparison of the toxicity of naphthalene and 1-methylnaphthalene.

One chronic study was located that documented the toxicity of naphthalene in rats (Schmahl 1955). No treatment-related effects were reported at a dose level of 41 mg/kg/day for 700 days. The study was not suitable as the basis for deriving a chronic MRL because only one dose level was evaluated, histopathological examination was limited, and dosing was not precisely controlled.

Death. The majority of human deaths following naphthalene intoxication have resulted from the intentional ingestion of mothballs. The reported case studies are descriptive in nature and do not provide sufficient information for an accurate determination of lethal doses. The death of an infant who wore diapers that had been stored in naphthalene mothballs has also been reported (Schafer 1951). No estimates of the naphthalene concentration were available.

Animal studies indicate that oral doses of naphthalene at 300-500 mg/kg/day are lethal to mice (Plasterer et al. 1985), but rats (Yamauchi et al. 1986) and rabbits (Rossa and Pau 1988) tolerated doses up to 1,000 mg/kg.

Based on the available data, the presence of naphthalene-containing consumer products in the home is associated with the greatest risk of lethality because of the possibility of intentional or accidental ingestion of naphthalene products, particularly by young children, or dermal and/or respiratory exposure of infants to naphthalene-treated clothing and other fabric articles. It seems less likely that environmental or workplace levels of naphthalene would reach concentrations high enough to pose a concern for lethality.

Single doses of 71-426 mg/kg 1-methylnaphthalene by intraperitoneal injection produced no mortalities in mice (Rasmussen et al. 1986), and oral exposure to as much as 143.7 mg/kg/day for 81 weeks was without effect on survival or longevity (Murata et al. 1993).

Intraperitoneal administration of a single dose of 2-methylnaphthalene to mice was not lethal at doses up to 800 mg/kg, but 20-40% of the dosed mice died at 1,000 mg/kg (Griffin et al. 1981, 1983). When 625 mg/kg of the glutathione-depleting agent (diethylmaleate) was administered 1 hour before 400 mg/kg 2-methylnaphthalene, the mortality rate was 80% (Griffin et al. 1982). Thus, the availability of systemic glutathione exerts a protective effect against the toxicity of 2-methylnaphthalene.

Systemic Effects

Respiratory Effects- No reports of human pulmonary toxicity after inhalation, oral, or dermal exposure to naphthalene were found. In animals, inhalation of 10 or 30 ppm naphthalene was associated with inflammation of the nose and lungs in mice and there was hyperplasia and metaplasia of the nasal cavity (NTP 1992a). Some studies have shown that the intraperitoneal administration of naphthalene (125-600 mg/kg) caused enlargement, exfoliation, and pulmonary necrosis of Clara cells in some strains of mice (Honda et al. 1990; Mahvi et al. 1976; O'Brien et al. 1989; Plopper et al. 1992a; Tong et al. 1981, 1982; Warren et al. 1982). Clara cells are rich in cytochrome P-450 enzymes (Plopper et al. 1992a, 1992b), and thus may be capable of producing cytotoxic metabolites of naphthalene. Because Clara cell damage has been reported to occur only in certain species or strains of animals following intraperitoneal administration, the relationship of this effect to potential human health effects is not evident.

There is no information available on the effects of human exposure to 1-methylnaphthalene or 2-methylnaphthalene on the respiratory system. A single intraperitoneal injection of 2-methylnaphthalene at 200 mg/kg resulted in slight exfoliation of bronchial epithelium in mice (Griffin et al. 1981) and 400-600 mg/kg resulted in severe exfoliation (Griffin et al. 1981, 1983; Honda et al. 1990). There were minimal or no effects on the lung epithelium with doses of 71-142 mg/kg although there was increased vacuolization of the Clara cells (Rasmussen et al. 1986).

The mechanism for 2-methylnaphthalene pulmonary toxicity seems to be slightly different from the naphthalene mechanism. Inducers and inhibitors of the microsomal mixed function oxidase system had a minimal effect on the Clara cell damage caused by 2-methylnaphthalene (Griffin et al. 1982, 1983), but they had a strong influence on the pulmonary toxicity of naphthalene (Warren et al. 1982). However, there was a direct relationship between the degree of metabolite binding in the lung and the cell damage for both naphthalene and 2-methylnaphthalene (Griffin et al. 1982, 1983; Warren et al. 1982).

1-Methylnaphthalene did not damage the lung epithelium of rats when doses of up to 142 mg/kg were given by intraperitoneal injection (Dinsdale and Verschoyle 1987) but there was increased vacuolization of the Clara cells in mice with a dose of 71 mg/kg (Rasmussen et al. 1986). At comparable molar doses, cytotoxicity of 1-methylnaphthalene in mice was about one fourth that caused

by naphthalene and 2-methylnaphthalene (Rasmussen et al. 1986). Chronic oral exposure to 71.6-143.7 mg/kg/day 1-methylnaphthalene was associated with pulmonary adenomas and/or alveolar proteinosis in male and female mice (Murata et al. 1993). Proteinosis incidence ranged from 8.2% to 10% in the controls and from 34.7% to 46.0% in the treated mice, respectively.

The observed effects of naphthalene, l-methylnaphthalene, and 2-methylnaphthalene on the lung epithelium suggest that chronic exposures of humans to these compounds might be matters of health concern. Based on limited data, Clara cells are most sensitive to naphthalene and least sensitive to 1 -methylnaphthalene,

Cardiovascular Effects. There is no information available on the cardiovascular effects of naphthalene in humans by any route or for any duration category.

In animals, no cardiovascular effects were seen in mice, rats, or rabbits following exposure to naphthalene.

No information is available that documented cardiovascular effects in humans following exposure to 1-methylnaphthalene by any route or for any duration category.

In mice, heart weights were significantly decreased after chronic oral exposure to I-methylnapththalene (Murata et al. 1993). No obvious changes in tissue histopathology were noted.

No information is available that documented cardiovascular effects in humans or animals following exposure to 2-methylnaphthalene.

Gastrointestinal Effects. Nausea, vomiting, abdominal pain, and diarrhea have been associated with ingestion of naphthalene in humans (Bregman 1954; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985).

In animals, no treatment-related effects on the gastrointestinal system were observed in mice or rats exposed to naphthalene after inhalation or oral exposure (Battelle 1980a, 1980b) except for one instance where stomach lesions and discolored intestines were seen in rats exposed to large doses during an LD_{50} study (Papciak and Mallory 1990).

No information was located that documented the gastrointestinal effects of 1-methylnaphthalene in humans by any route or for any duration category.

In mice exposed to doses of up to 143.7 mg/kg/day 1-methylnaphthalene for 81 weeks, there were no observable effects on the stomach and intestines (Murata et al. 1993).

No information was located that documented the gastrointestinal effects of 2-methylnaphthalene in humans or animals by any route or for any duration category.

Hematological Effects. It is clear that a primary target of naphthalene toxicity in humans is the erythrocyte. All reports of human toxicity feature hemolytic crises (Dawson et al. 1958; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; MacGregor 1954; Mackell et al. 1951; Ojwang et al. 1985; Schafer 1951; Shannon and Buchanan 1982; Valaes et al. 1963). Hemolytic anemia is characterized by findings of lowered hemoglobin, hematocrit, and erythrocyte values, elevated reticulocyte counts, Heinz bodies, elevated serum bilirubin; and fragmentation of erythrocytes (Dawson et al. 1958; Valaes et al. 1963; Zuelzer and Apt 1949). In patients who developed severe hemolytic anemia after exposure to naphthalene, treatment with blood transfusions was effective.

A relationship appears to exist between an inherited G6PD deficiency and susceptibility to naphthalene-induced hemolysis (Dawson et al. 1958; Shannon and Buchanan 1982; Valaes et al. 1963). However, this trait is not a prerequisite for the hemolysis, because hemolysis also occurs in unaffected individuals. Individuals with G6PD deficiency are susceptible to hemolysis induced by numerous pharmaceutical or chemical agents. Infants appear to be particularly sensitive to the hemolytic effects of naphthalene. Naphthalene sensitivity in newborns may be due to the infant's decreased ability to conjugate and excrete naphthalene metabolites (Valaes et al. 1963). Hemolysis is a health concern for individuals who may be exposed to naphthalene through its presence at hazardous waste sites, particularly for infants and young children with a G6DP deficiency.

Red cell hemolysis was not observed in studies of common laboratory animals. CD-l mice receiving oral doses of naphthalene up to 267 mg/kg/day for 14 days or up to 133 mg/kg/day for 90 days did not develop hemolytic anemia (Shopp et al. 1984). However, rats and mice appear to be relatively resistant to red cell hemolysis when compared to humans and dogs. Hemolytic effects were reported in a dog receiving a single 1,525 mg/kg dose in food and in another dog receiving approximately

263 mg/kg/day in food for 7 days. Thus, rats and mice may not be appropriate models for studying the hemolytic effects of naphthalene.

Exposure to a mist of pure 1-methylnaphthalene dissolved in kerosene on 4 consecutive mornings increased reticulocytes in splenectomized dogs. Practical grade compound had no effect on reticulocytes but increased both the leukocytes and neutrophils in intact dogs and leukocytes in splenectomized dogs. No effects were observed on hemoglobin or hematocrit (Lorber 1972). After chronic oral exposure to 1-methylnaphthalene, female mice exhibited increases in hemoglobin, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (Murata et al. 1993). The males were not affected. The significance of these effects is not clear, but may be relevant for humans who developed anemia after naphthalene exposure (Harden and Baetjer 1978).

2-Methylnaphthalene had no effect on any hematological parameters in dogs exposed through a fogging apparatus (Lorber 1972).

Musculoskeletal Effects. No information was located that documented musculoskeletal effects of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene in humans or animals by any route or duration category.

Hepatic Effects. Varying degrees of jaundice and liver enlargement were reported in humans with hemolytic anemia after oral (Bregman 1954; Chusid and Fried 1955; Gidron and Leurer 1956; Gupta et al. 1979; Kurz 1987; Ojwang et al. 1985), inhalation (Valaes et al. 1963), or dermal exposure (Dawson et al. 1958; Schafer 1951) to naphthalene. Jaundice is frequently the cause of hospitalization and is apparent before the detection of hemolysis (Valaes et al. 1963). Both the jaundice and the increased liver size may be related to an indirect effect of hemolysis rather than a direct hepatic toxicological effect associated with naphthalene exposure.

A positive association between the incidence of severe neonatal jaundice in Nigerian infants and use of naphthalene in the home has been reported (Familusi and Dawodu 1985). The levels of exposure were not defined and the routes of exposure may have been inhalation, oral, or dermal. Naphthalene exposure may have resulted from the use of mothballs and insecticides or from the use of traditional home remedies such as lotions, topical antiseptics, or cough preparations to which naphthalene was intentionally added. Households that used naphthalene were compared with those that did not.

The liver was also demonstrated to be a target organ for naphthalene toxicity in animal studies. Repeated oral doses of naphthalene (750-1,000 mg/kg/day) produced increased liver weights, increased aniline hydroxylase activity, and increased levels of lipid peroxides in rats (Germansky and Jamall 1988; Rao and Pandya 1981; Yamauchi et al. 1986). In mice, activities of benzo(a)pyrene hydroxylase were decreased with 90-day exposures to 53 and 133 mg/kg/day naphthalene and aniline hydroxylase activity was increased by a dose of 133 mg/kg/day (Shopp et al. 1984). These data indicate that intermediate and possibly chronic exposures to naphthalene in the environment might compromise the ability of the liver to metabolize other xenobiotics and thus be a matter of health concern. Decreases in BUN in female mice and the BUN/creatinine ratio in male and female mice support the conclusion that hepatic metabolic function is affected by continuous exposure to naphthalene (Shopp et al. 1984). These effects were used as the basis of the intermediate duration oral MRL.

There is no information available on the hepatic effects of human exposure to 1-methylnaphthalene by any route of exposure.

There were no effects on mouse liver histopathology after an intraperitoneal dose of 426 mg/kg 1-methylnaphthalene (Rasmussen et al. 1986) or oral exposure up to 143.7 mg/kg/day for 81 weeks (Murata et al. 1990). There were no significant changes in liver/body weight ratio, microsomal proteins, or the *O*- and *N*-demethylation of p-nitroanisole and aminopyrene with an intraperitoneal dose of 100 mg/kg 1-methylnaphthalene (Fabacher and Hodgson 1977).

There is no information available on the hepatic effects of human exposure to 2-methylnaphthalene by any route of exposure.

The information available from animal studies does not suggest that hepatic effects are of potential concern. A single intraperitoneal injection of 2-methylnaphthalene at doses up to 1,000 mg/kg in mice did not result in observable microscopic abnormalities of the liver (Griffin et al. 1981, 1983).

There were no significant changes in mouse liver/body weight ratio, microsomal proteins, or the 0- and N-demethylation of p-nitroanisole and aminopyrene with an intraperitoneal dose of 100 mg/kg 2-methylnaphthalene (Fabacher and Hodgson 1977). Glutathione depletion, however, was apparent in the liver at a dose of 400 mg/kg (Griffin et al. 1982, 1983). A hepatic deficiency of glutathione would

leave the liver vulnerable to exposure from agents that are conjugated with glutathione as a detoxification mechanism and would reduce free radical defenses that use glutathione peroxidase.

Renal Effects. Evidence of renal involvement, especially proteinuria, has been reported in humans after the oral ingestion of toxic doses of naphthalene (Gupta et al. 1979; Kurz 1987; Ojwang et al. 1985). These changes may have been secondary to hemoglobinuria resulting from hemolysis. Proximal tubule damage and general tubular necrosis were observed at autopsy of two poisoning victims (Gupta et al. 1979; Kurz 1987).

Renal effects have not been reported in animal studies. There was no significant evidence of renal toxicity in laboratory animals (rats and mice) treated with naphthalene at various dosage levels (133-1,000 mg/kg/day) and durations of exposure (10-90 days) by the oral route (Battelle 1980a, 1980b; Rao and Pandya 1981).

There were no data available related to the renal effects of 1-methylnaphthalene in humans by any route of exposure.

There were no histopathological changes in the kidneys of mice given 426 mg/kg 1-methylnaphthalene by intraperitoneal injection (Rasmussen et al. 1986). Chronic oral exposure to 71.6 or 140.2 mg/kg/day 1-methylnaphthalene was associated with an increase in kidney weights in male mice, with no evidence of histological abnormalities (Murata et al. 1993).

No studies were located relating to the potential renal effects of human exposure to 2-methylnaphthalene by any route, and the information available from animal studies does not suggest that this compound is a renal toxicant. In mice, a single intraperitoneal injection of 2-methylnaphthalene at doses up to 1,000 mg/kg did not result in observable microscopic abnormalities of the kidney (Griffin et al. 1981, 1983).

Renal effects as a consequence of exposure to naphthalene, l-methylnaphthalene, or 2-methylnaphthalene in the environment do not seem to be a matter of public health concern.

Dermal Effects. No information was located that documented dermal effects of naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene in humans by any route of exposure.

A study in rabbits has shown that naphthalene is a mild dermal irritant, causing erythema and fissuring, when directly applied to the shaved, abraded or nonabraded skin under a dressing; healing occurred within 6-7 days (Papciak and Mallory 1990; PRH 1985a). In rats that were dermally treated for 6 hours/day, 5 days per week, for 13 weeks with 1,000 mg/kg/day naphthalene, there was an increased incidence of excoriated skin lesions and papules (Prantz et al. 1986). However, similar lesions were seen in the controls and lower dose group animals. At the high dose the naphthalene appeared to exacerbate the severity of the lesions. Acute and chronic exposure of animal skin to naphthalene appears to cause dermal irritation.

Ocular Effects. Equivocal evidence of cataract formation has been reported in a limited number of humans who were occupationally exposed to naphthalene vapors, who had accidental ocular contact with naphthalene crystals, or who consumed naphthalene (5 g) as a medication (Ghetti and Mariani 1956; Lezenius 1902; van der Hoeve 1906). In all cases, concurrent exposure to other chemicals was possible. Thus it is difficult to determine if naphthalene exposure through its presence at hazardous waste sites has any cataractogenic potential.

Cataract formation following naphthalene exposure (50s1,000 mg/kg/day) has been reported in rabbits (Srivastava and Nath 1969; van Heyningen and Pirie 1967, 1976) and less frequently in rats (Murano et al. 1993; Yamauchi et al. 1986) and mice (Shichi et al. 1980). Uyama et al. (1955) reported the excretion of beta-naphthoquinone in the urine of naphthalene-treated rabbits and that 1 ,2-naphthoquinone produced cataracts in scorbutic guinea pigs. Van Heyningen and Pirie (1967) have speculated that 1,2-naphthoquinone may be responsible for the cataractogenic effect of naphthalene in rabbits.

Continued administration of naphthalene (500 mg/kg/day) to rats for up to 5 weeks led to additional damage to the eye with destruction of the photoreceptors of the retina, proliferation of the retinal pigment epithelium, and subretinal vascularization of (Grzalesi et al. 1993). These changes are unlikely to be matters of human health concern at hazardous waste sites because they apparently only result from continuous exposure to large doses of naphthalene.

There were no data available related to the ocular effects of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals by any route of exposure.

Body Weight Effects. Studies in humans did not reveal any effects of naphthalene on body weight. However, in several animal studies, feeding of naphthalene led to decreases in body weight gain (Battelle 1980b; Shopp et al. 1984).

There are no data available the effects of 1-methylnaphthalene in humans by any route of exposure. In mice, chronic exposure occurring over an 81l-week period had no effect on body weight (Murata et al. 1993).

There were no data available related to the effects of 2-methylnaphthalene on body weight in humans or animals by any route of exposure.

Other Systemic Effects. Elevated body temperatures were seen in human subjects after exposure to naphthalene by both the oral and dermal routes (Chusid and Fried 1955; Gidron and Leurer 1956; Haggerty 1956; Kurz 1987; MacGregor 1954; Ojwang et al. 1985). However, bacterial infections may have been the cause of the fever in some situations (Kurz 1987; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985).

Clinical signs of neurotoxicity were observed in pregnant rats that were exposed to 50 mg/kg/day naphthalene over a 10-day period. These effects were used as the basis of the acute duration oral MRL. Acclimatization to the naphthalene occurred over a period of 2-3 days after the onset of dosing. There were no other reports of neurotoxicity in animal studies.

Immunological and Lymphoreticular Effects. No reports of immunological or lymphoreticular effects of naphthalene in humans were found, and only limited information was identified from studies conducted on laboratory animals. Hemolysis accompanied by splenic enlargement, in a case study (Gidron and Leurer 1956), is considered a hematological effect (see Section 2.2).

Naphthalene did not alter humoral and cell-mediated immune response in mice administered oral doses for up to 90 days (Shopp et al. 1984). However, there may be some effects of naphthalene on the thymus in animals. After 14 days, thymus weights were reduced approximately 30% in male mice. No differences were noted in either sex when a lower dose was given for 13 weeks (Shopp et al. 1984). There was lymphoid depletion of the thymus in 2 of 10 female rats exposed to 400 mg/kg/day naphthalene for 13 weeks (Battelle 1980b).

In mice, spleen weights were reduced approximately 20% in female mice exposed to 267 mg/kg/day naphthalene for 14 days and 25% in females exposed to 133 mg/kg/day for 13 weeks (Shopp et al. 1984). However, there appeared to be no subsequent effect on immunocompetence. Based on in vitro the lack of immunosuppression activity may be due to the inability of the splenocyte to metabolize naphthalene (Kawabata and White 1990). When isolated splenic cells were incubated with 1-naphthol, 1,4-naphthoquinone, naphthalene-plus-liver microsomes, or naphthalene alone, antibody-forming cell response of the splenic cells was diminished by the exposure to the naphthalene metabolites and the naphthalene-plus liver microsomes, but not by naphthalene alone. Splenic microsomes are apparently not able to produce the naphthalene metabolites that can reduce the antibody-forming response by this organ.

There were no data available related to the immunological or lymphoreticular effects of l-methylnaphthalene in humans by any route of exposure. Gral exposure to 1-methylnaphthalene caused a dramatic increase in monocytes in male and female mice (Murata et al. 1993). The significance of this effect is not clear, but it may have been a physiological response to alveolar proteinosis.

There were no data available related to the immunological or lymphoreticular effects of 2-methylnaphthalene in humans or animals by any route of exposure.

Neurological Effects. Although there is some evidence of neurological effects associated with human exposure to naphthalene, these effects seem to be caused by oxygen deprivation due to red cell hemolysis and decreased oxygen transport. Nonspecific symptoms of confusion, lethargy, listlessness, and vertigo have been reported in humans exposed by inhalation to naphthalene (Linick 1983) and in persons who ingested large doses of naphthalene (Bregman 1954; Chusid and Fried 1955; Gupta et al. 1979; Kurz 1987; MacGregor 1954; Ojwang et al. 1985; Zuelzer and Apt 1949). Neurological symptoms are resolved as red blood cell counts and oxygen transport return to normal.

Clinical signs of toxicity were observed in gravid rats that were exposed to 50 mg/kg/day naphthalene over a 10-day period. These effects were used as the basis of the acute duration oral MRL. Acclimitization to naphthalene administration occurred over a 2-3 day period. No other reports of neurotoxicity in animal studies were located.

No studies were located that documented neurological effects of 1-methylnaphthalene in humans by any route of exposure.

In male mice, slight but statistically significant increases in relative brain weights occurred after chronic exposure to up to 140.2 mg/kg/day 1-methylnaphthalene in the diet. No tissue or cellular abnormalities were observed (Murata et al. 1993).

No studies were located that documented neurological effects of 2-methylnaphthalene in humans or animals by any route of exposure.

Reproductive Effects. No studies were located on the reproductive effects of naphthalene in humans. The results of animal studies, however, suggest that this may be an area of concern. Reduced numbers of mouse pups per litter were observed when naphthalene in corn oil was orally administered to pregnant mice (Plasterer et al. 1985); but no effects were seen when pregnant rabbits were orally administered naphthalene at even higher doses but delivered in methylcellulose rather than in an oil vehicle (PRI 1986). These differences could be due to species sensitivity or to the vehicle used to deliver naphthalene. However, these observations demonstrate the importance of vehicle selection and bioavailability in any further toxicity studies that might be conducted with naphthalene. In an in vitro assay of embryotoxicity, naphthalene did not effect blastocyst development when concentrations of from 0 to 0.78 mM were added to the medium; but when both naphthalene and liver microsomes were added, embryonic viability was significantly reduced at the lowest concentration tested (0.16 mM) (Iyer et al. 1991). A concentration of 0.2 mM was associated with 100% embryonic mortality. These results suggest that microsomal naphthalene metabolites may be responsible for embryotoxicity, and support the hypothesis that a medium that decreased naphthalene bioavailability would also reduce its toxicity during the early stages of reproduction.

Intraperitoneal administration of 500 mg/kg/day naphthalene resulted in a 53% depletion of epididymal glutathione levels relative to control groups. Testicular glutathione levels were not significantly affected (Gandy et al. 1990). Accordingly, reduced glutathione levels may be a factor in naphthalene-induced gene cell mutations and should be considered in the overall assessment of the potential reproductive toxicity of naphthalene.

Developmental Effects. The exposure of pregnant humans to high levels of naphthalene could result in-r fetal toxicity. Transplacental exposure of the fetus to naphthalene that had been ingested by the mother has resulted in neonatal hemolytic anemia (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). Developmental effects resulting from naphthalene exposure have not been observed in the limited animal data available. No fetal anomalies were observed when naphthalene was administered by gavage to pregnant mice (Plasterer et al. 1985) or by intraperitoneal injection to pregnant rats (Hardin et al. 1981).

No studies were located that documented developmental effects of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals by any route of exposure.

Genotoxic Effects. No studies of genotoxic effects in humans or laboratory animals were located.

In *vitro* data, presented in Table 2-4, suggest that genotoxicity is not an area of concern for exposure to naphthalene. Naphthalene exposure was not associated with increased incidences of sister chromatid exchange, or changes in the mitotic or proliferative indices, in microsomal-activated human peripheral lymphocytes (Tingle et al. 1993). Naphthalene did not cause cell transformations in rodent embryo cells (Freeman et al. 1973; Rhim et al. 1974) or in a murine mammary gland organ culture system (Tonelli et al. 1979). Naphthalene did not induce gene mutations in several bacteria/microsoma1 assay systems, including Salmonella tester strains TA 97, 98, 100, 677, 1535, or 1537, in the absence or presence of Aroclor 1254-induced hamster or rat liver microsomes (Bos et al. 1988; Connor et al. 1985; Florin et al. 1980; Gatehouse 1980; Kaden et al. 1979; McCann et al. 1975; Mortelmans et al. 1986; NTP 1992a; Sakai et al. 1985; Seixas et al. 1982). There was also no evidence of DNA damage in *Escherichia coli* WP2/WPl00 (Mamber et al. 1983) or GY5027/GY4015 (Mamber et al. 1984) and *Salmonella typhimurium* TA 1535/p5K 1002 (Nakamura et al. 1987). Similarly, results were negative in rat hepatocyte cultures evaluated to determine the potential for naphthalene to induce DNA damage (Sina et al. 1983). Naphthalene caused sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (NTP 1992a).

No studies were located that documented genotoxic effects of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals by any route of exposure. Data are limited to one *in vitro* study where 1-methylnaphthalene and 2-methylnaphthalene failed to induce chromosomal aberration in human peripheral lymphocytes (Kulka et al. *1988).* In an *in vitro* microbial assay employing

TABLE 2-4. Genotoxicity of Naphthalene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Naphthalene				
Prokaryotic organisms: *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	McCann et al. 1975
S. typhimurium (TA98, TA100, UTH8414, UTH8413)	Gene mutation	–	–	Connor et al. 1985
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	NTP 1992a
S. typhimurium (TA1535, TA1537, TA97, TA98, TA100)	Gene mutation	–	–	Mortelmans et al. 1986
S. typhimurium (TA157, TM677)	Gene mutation	–	–	Seixas et al. 1982
S. typhimurium (TA98, TA100)	Gene mutation	–	No data	Bos et al. 1988
S. typhimurium (TA97, TA98, TA100)	Gene mutation	–	–	Sakai et al. 1985
S. typhimurium (TA1537, TA1538)	Gene mutation	–	No data	Gatehouse 1980
S. typhimurium (TM677)	Gene mutation	–	No data	Kaden et al. 1979
Escherichia coli WP2/WP100 (uvrA recA)	DNA damage/repair	–	No data	Mamber et al. 1983
E. coli (GY5027 en VA' uVrB'; GY4015 amp)	DNA damage	–	No data	Mamber et al. 1984
S. typhimurium (TA1535/pSk1002)	DNA damage	–	–	Nakamura et al. 1987

TABLE 2-4. Genotoxicity of Naphthalene *In Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Mammalian cells:				
Rat hepatocyte/ alkaline elution	DNA damage	–[a]	No data	Sina et al. 1983
Rat hepatocyte primary culture	DNA repair		–	PRI 1985e
Mouse mammary gland	Cellular transformation		–	Tonelli et al. 1979
Rat embryo cell culture	Cellular transformation		–	Freeman et al. 1973
Chinese hamster ovary cells	Sister chromatid exchange	±	+	NTP 1992a
Chinese hamster ovary cells	Chromosomal aberration	+	–	NTP 1992a
Mouse bone marrow	Micronuclei		–	PRI 1985d

[a] Exogenous activation not required.

– = negative result; ± = positive and negative results; + = positive result; DNA = deoxyribonucleic acid

S. ryphimurium, mutagenic activity was not detected with either compound, with either the presence or absence of microsomal activation (Florin et al. 1980). These studies are presented in Table 2-5.

Cancer. No epidemiology studies of carcinogenesis related to naphthalene exposure were located.

Data available from animal studies do not agree regarding the carcinogenic effects resulting from naphthalene exposure. There was some evidence of carcinogenic activity of naphthalene in female $B6C3F_1$ mice as characterized by a statistically significant increased incidence of pulmonary alveolar/bronchiolar adenomas in the high dose group (30 ppm) following exposure to the compound for 2 years (NTP 1992a). The EPA has classified naphthalene as a Group D carcinogen (not classifiable as to human carcinogenicity) based on the absence of animal data. Final results of the NTP bioassay are being reviewed by EPA.

In the strain A mouse lung tumor inhalation bioassay, a significant increase in the number of tumors per tumor-bearing mouse was noted, but the number of mice with tumors was not significantly increased in animals exposed to 10 or 30 ppm naphthalene for 6 months (Adkins et al. 1986). These results are considered equivocal because the incidence of adenomas in the control group for the naphthalene experiment was significantly lower than the incidence observed in historic control groups. No tumors were observed in rats administered naphthalene at 41 mg/kg/day in a 2-year feeding study (Schmahl 1955). There was no increase in the number of glutamyl transpeptidase foci in the livers of rats administered 100 mg/kg/day naphthalene intragastrically after prior treatment with phenobarbital, a stimulator of the microsomal mixed function oxidase system (Tsuda et al. 1980). Cells that stain positive for glutamyl transpeptidase are considered to be biomarkers of preneoplastic change. Thus, naphthalene does not appear to be a potential liver carcinogen. This assessment is supported by bioassay results (Adkins et al. 1986; NTP 1992a; Schmahl 1955).

The naphthalene lung tumor data in the absence of distinct evidence that naphthalene is genotoxic, can be explained by the hyperplasia seen in the epithelium of the respiratory track. Rapid cell division in response to tissue injury can lead to tumorigenesis when precancerous cells present in tissue are stimulated to divide. The observation of Adkins et al. (1986) that there was an increased incidence of tumors in each tumor bearing mouse, but not in the numbers of mice with tumors, supports classifying naphthalene as a promoter for lung tumors rather than a carcinogen. If this hypothesis is correct,

TABLE 2-5. Genotoxicity of 1-Methylnaphthalene and 2-Methylnaphthalene *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
1-Methylnaphthalene				
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Florin et al. 1980
2-Methylnaphthalene				
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Florin et al. 1980
Mammalian cells:				
Human lymphocytes (1-ME)	Chromosomal aberration	–	–	Kulka et al. 1988
Human lymphocytes (2-ME)	Chromosomal aberration	–	–	Kulka et al. 1988

– = negative result; 1-ME = 1-methylnaphthalene; 2-ME = 2-methylnaphthalene

naphthalene is of greatest environmental concern when exposure to naphthalene is accompanied by exposure to pulmonary carcinogens.

No studies were located that documented cancer effects of 1-methylnaphthalene in humans by any route of exposure. Chronic oral exposure to l-methylnaphthalene for 81 weeks did not increase the incidence of carcinomas in mice, but did result in a statistically significant increase in the incidence of pulmonary adenomas in male mice exposed to 71.6 or 140.2 mg/kg/day in the diet (Murata et al. 1993). Regenerative hyperplasia induced by Clara cell exfoliation and the production of oxidized naphthalene metabolites in the lungs may have contributed to the development of pulmonary adenomas in exposed mice. Thus, chronic exposure to 1-methylnaphthalene may be an issue of pulmonary human health concern.

No studies were located that documented cancer effects of 2-methylnaphthalene in humans or animals by any route of exposure.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are

commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to naphthalene are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by naphthalene are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

Additional information concerning biomarkers for effects on the immune, renal, and hepatic systems can be found in the CDC/ATSDR Subcommittee Report on Biological Indicators of Organ Damage (CDC/ATSDR 1990), and on the neurological system in the Office of Technology Assessment Report on Identifying and Controlling Poisons of the Nervous System (OTA 1990). Additional details concerning the health effects caused by naphthalene can be found in Section 2.2.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

In cases where humans have swallowed one or more mothballs, it is possible to identify the undissolved naphthalene in the stomach or duodenum by radioluminescence (Woolf et al. 1993). Thus, radiography of the abdominal area is of value in determining if exposure has occurred, especially in children who are often unreliable sources of exposure information. Of the 2,400 cases on naphthalene ingestion reported to 72 Poison Control Centers in the United States, 2,100 involve children less than 6 years old. Radioluminescence has the advantage of differentiating

naphthalene-containing solids in the gastrointestinal tract from paradichlorobenzene or other materials used in moth repellants and deodorizers.

Methods are available for the determination of naphthalene in human adipose tissue (Liao et al. 1988; Stanley 1986). In the National Human Adipose Tissue Survey, 40% of the subjects surveyed had measurable levels of naphthalene with concentrations of up to 63 rig/g. Naphthalene and its metabolites can be detected in human and animal urine (Homing et al. 1980; Mackell et al. 1951; Stillwell et al. 1982). Investigators have reported strong correlations between I-naphthol concentrations in the urine of exposed workers and naphthalene concentrations in the breathing zone air (Bieniek 1994). Peak naphthalene concentrations in the urine occurred immediately after the end of the exposure period and declined thereafter. In some instances 1-naphthol concentrations had returned to baseline 8 hours later. Few current data are available relating naphthalene levels in adipose tissue or urine with the human exposure concentrations.

In swine a good correlation existed between 1-naphthol levels in hydrolyzed urine samples collected in the first and second 24 hours after dosing with as little as 7 μg/kg/day naphthalene (Keimig and Morgan 1986). Thus, 1-naphthol may be an appropriate biomarker for monitoring naphthalene exposures in the occupational setting. Some caution must be exercised in using 1-naphthol as a biomarker of naphthalene exposure in the general population since this metabolite is also excreted after exposure to the common insecticide, carbaryl (Benson and Dorough 1983).

Immunological techniques are being developed for identification of naphthalene mercapturic acid derivatives in urine (Marco et al. 1993) and naphthalene hemoglobin adducts in blood (Cho et al. 1994b). These techniques are not yet fully perfected or available for clinical use. The hemoglobin adduct assay is only appropriate for situations where exposure to large quantities of naphthalene has occurred. Adducts form at exposure concentrations that exceed the availability of glutathione for conjugation.

An analytical method is available to determine levels of 2-methylnaphthalene and its derivatives in rat urine (Melancon et al. 1982). This method would probably also be useful in measuring 2-methylnaphthalene levels in human urine. Because of the lack of information for l-methylnaphthalene, it is not possible to identify a biomarker of exposure for this substance.

2.5.2 Biomarkers Used to Characterize Effects Caused by Naphthalene, 1 -Methylnaphthalene, and 2-Methylnaphthalene

Hemolytic anemia has been frequently reported to be a consequence of exposure to naphthalene. However, this effect can also occur without exposure to naphthalene, and may not be useful as a specific biomarker of effect.

Clara cell damage may be identified by the presence of naphthalene/protein adducts in lung lavage fluids (Cho et al. 1994a). Additional research is needed to improve the specificity of this technique as a biomarker of effect.

Because of the lack of information for 1-methylnaphthalene or 2-methylnaphthalene, it is not possible to identify a biomarker of effects for these chemicals.

2.6 INTERACTIONS WITH OTHER SUBSTANCES

When either naphthalene, l-methylnaphthalene, or 2-methylnaphthalene was applied dermally in combination with benzo[a]pyrene (BaP), there was an inhibitory effect on the induction of skin tumors in female mice (Schmeltz et al. 1978). These investigators also reported that a mixture containing naphthalene (0.02%), 2-methylnaphthalene (0.02%) and 10 other methylated and ethylated naphthalenes (each at 0.02%) also appeared to inhibit the development of BaP-induced skin tumors. The authors suggested that it is likely that certain naphthalenes compete with BaP for the same enzyme sites, resulting in alteration of the BaP metabolic pathway and decreased production of the active BaP metabolite. This hypothesis is consistent with the observation that benzo(a)pyrene hydroxylase is inhibited by naphthalene (Shopp et al. 1984). Dermal application of the naphthalene mixture did not induce tumors in the absence of BaP. The results of these studies were not analyzed statistically.

Several studies have been conducted to assess factors which influence the toxicity of naphthalene. For the most part, these studies have evaluated the effects of mixed function oxidase activity (MFO) and alterations in glutathione levels on pulmonary and ocular toxicities. The effects of cyclooxygenase activity, antioxidants, and epoxide hydrolase inhibitors on the cataractogenic effect of naphthalene have also been evaluated. The administration of MFO inhibitors (SKF-525A, metyrapone) and antioxidants

(caffeic acid and vitamin E) decreased ocular toxicity in mice (Wells et al. 1989). Use of ALO1576, an inhibitor of the enzyme aldose reductase, prevented cataract formation in both in vivo and in vitro studies (Xu et al. 1992a, 1992b). On the other hand, naphthalene-induced cataracts were enhanced by pretreatment with a MFO inducer (phenobarbital) and a glutathione depletor (diethyl maleate) (Wells et al. 1989). Pulmonary damage was decreased by prior treatment with a MFO inhibitor (piperonyl butoxide), but enhanced by prior treatment with a glutathione depletor (diethyl maleate) (Warren et al. 1982). For the most part, these studies support the role for mixed function oxidase activity and glutathione conjugation in naphthalene-induced pulmonary and ocular lesions.

Mixed function oxidase inducers also affect the metabolism of 2-methylnaphthalene. Inducers that influence cytochrome P-450 increase the oxidation of the side chain and the concentration of one dihydrodiol. Induction of cytochrome P-450 increased the production of two other dihydrodiols (Melancon et al. 1985). The production of naphthoic acid in preference to the diols may explain why 2methylnaphthalene is less toxic to Clara cells than naphthalene.

In general, interactions with environmental contaminants, such as polycyclic aromatic hydrocarbons, should be expected at hazardous waste sites. Most hazardous waste sites (with the notable exception of certain pharmaceutical sites) would not be expected to contain substantial volumes of certain types of contaminants, such as antioxidants or cytochrome P-450 inhibitors.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to naphthalene than will most persons exposed to the same level of naphthalene in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, “Populations With Potentially High Exposure.”

The hemolytic response to naphthalene is enhanced by the presence of inherited erythrocyte G6PD deficiency. Although any human may experience acute hemolysis if exposed to a sufficiently high dose of naphthalene, this enzyme deficiency may cause some persons to be unusually sensitive. The incidence of the deficiency among Caucasians of European origin is relatively low, while there is a higher incidence among certain groups of Asians and Middle Eastern populations. A study of hemolytic anemia in African-American children with G6PD deficiency by Shannon and Buchanan (1982) suggests that this is a population that may be susceptible to the hemolytic effects of naphthalene exposure. It was also reported that 16% of African-American males are G6PD-deficient (Calabrese 1986). According to Shannon and Buchanan (1982), a syndrome of acute severe hemolysis following exposure to oxidative stress is associated with the Mediterranean variant of the deficiency, whereas the hemolytic anemia seen in African-Americans is generally mild.

Infants also appear to be more sensitive to the effects of naphthalene than adult humans. It is believed that the less-developed metabolic conjugation pathways of the infant may contribute to its sensitivity to naphthalene. The limited mobility of infants when they are wearing naphthalene-treated clothing or when they are near other naphthalene-treated articles may maximize exposure due to the development of a microenvironment with a high level of naphthalene vapor in the space around the infant. The tendency for infants and small children to place small objects, such as mothballs, in their mouths also increases their risk.

There are no data that indicate whether there are populations that are unusually susceptible to the toxic effects of 1-methylnaphthalene and 2-methylnaphthalene.

2.8 METHODS OF REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to naphthalene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to naphthalene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

If inhalation of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene has occurred, movement to fresh air is recommended. In cases where a small amount (e.g., 1 mothball, 0.5-3.6 g) of naphthalene has been ingested, measures are implemented to empty the stomach contents. Syrup of Ipecac, which may be used for this purpose, is administered after ingestion to induce vomiting and is most effective if initiated within a 2 hour period after exposure (Siegel and Wason 1986). If large quantities of naphthalene have been ingested, syrup-of-ipecac-induced vomiting is usually followed by gastric aspiration using a large gauge lavaculator (to remove mothballs) (Kurz 1987). This will only be of value if the naphthalene particles are small enough to be aspirated. Measures are usually taken to protect the respiratory tract from aspiration of gastric contents. Activated charcoal can be given to bind dissolved naphthalene in the gastrointestinal tract. Further treatment with a cathartic (e.g., magnesium sulfate) to speed fecal excretion is recommended (Melzer-Lange and Walsh-Kelly 1989). Milk or fatty meals ingested within 2-3 hours after exposure may increase absorption (Siegel and Wason 1986).

In order to reduce absorption of naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene through the skin, areas of skin that have come in contact with the compound should be washed with soap and water. Application of oil based lotions should be avoided. If these compounds are splashed into the eyes, irrigation with large amounts of water for 15-30 minutes is recommended (Stutz and Janusz 198s).

2.8.2 Reducing Body Burden

Some evidence exists that naphthalene metabolites may be retained in the body in adipose tissue (Stanley 1986). Naphthalene was identified in 40% of the samples evaluated for the Human Adipose Tissue Survey (Stanley 1986). Naphthalene metabolites were detected in urine up to 13 days following exposure (Mackell et al. 1951).

The most significant toxic effect of naphthalene in humans is red cell hemolysis. In cases of clinically significant hemolysis, accelerated urinary excretion of naphthol metabolites is recommended to protect the kidney from products of hemolysis (EPA 1989d). In cases of renal failure, hemodialysis may be effective in controlling extracellular fluid (plasma) composition (EPA 1989d). It should be noted that

this method is not very effective in removing hpophilic compounds from blood. Ocular effects have also been reported in humans; however, there are no specific treatments for reducing the toxic effects on the eyes. Pulmonary effects have been observed in animals but these effects have not been reported in humans. Due to lack of data, it is difficult to speculate regarding the benefits of treatments that enhance elimination of naphthalene, l-methylnaphthalene, and 2-methylnaphthalene and their metabolites as a basis for reducing toxic effects.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Existing data indicate that lung and eye toxicity are mediated by reactive intermediates for both naphthalene and 2-methylnaphthalene. Current data suggest that the Liver may form a precursor metabolite or reactive metabolite that is transported to the lungs and eyes (Buckpitt and Warren 1983; Van Heyningen and Pirie 1967). More information is needed on the bioactivation of naphthalene and transport mechanisms before methods for blocking those mechanisms can be developed.

Many of the symptoms of naphthalene poisoning in humans are a direct consequence of red blood cell hemolysis. Blood transfusions, packed red blood cell transfusions, and exchange transfusions (particularly in infants) can be used to replenish the concentration of red blood cells and diminish the risks of cellular anoxia (Bregman 1954; Chusid and Fried 1955; MacGregor 1954; Mackell et al. 1951). Bicarbonate is also administered to hemolysis patients to increase the alkalinity of the urine and thereby minimize deposition of hemoglobin in the kidney tubules (Chusid and Fried 1955; Gidron and Leurer 1956).

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of naphthalene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of naphthalene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of Naphthalene, 1-Methylnaphthalene, and 2-Methylnaphthalene

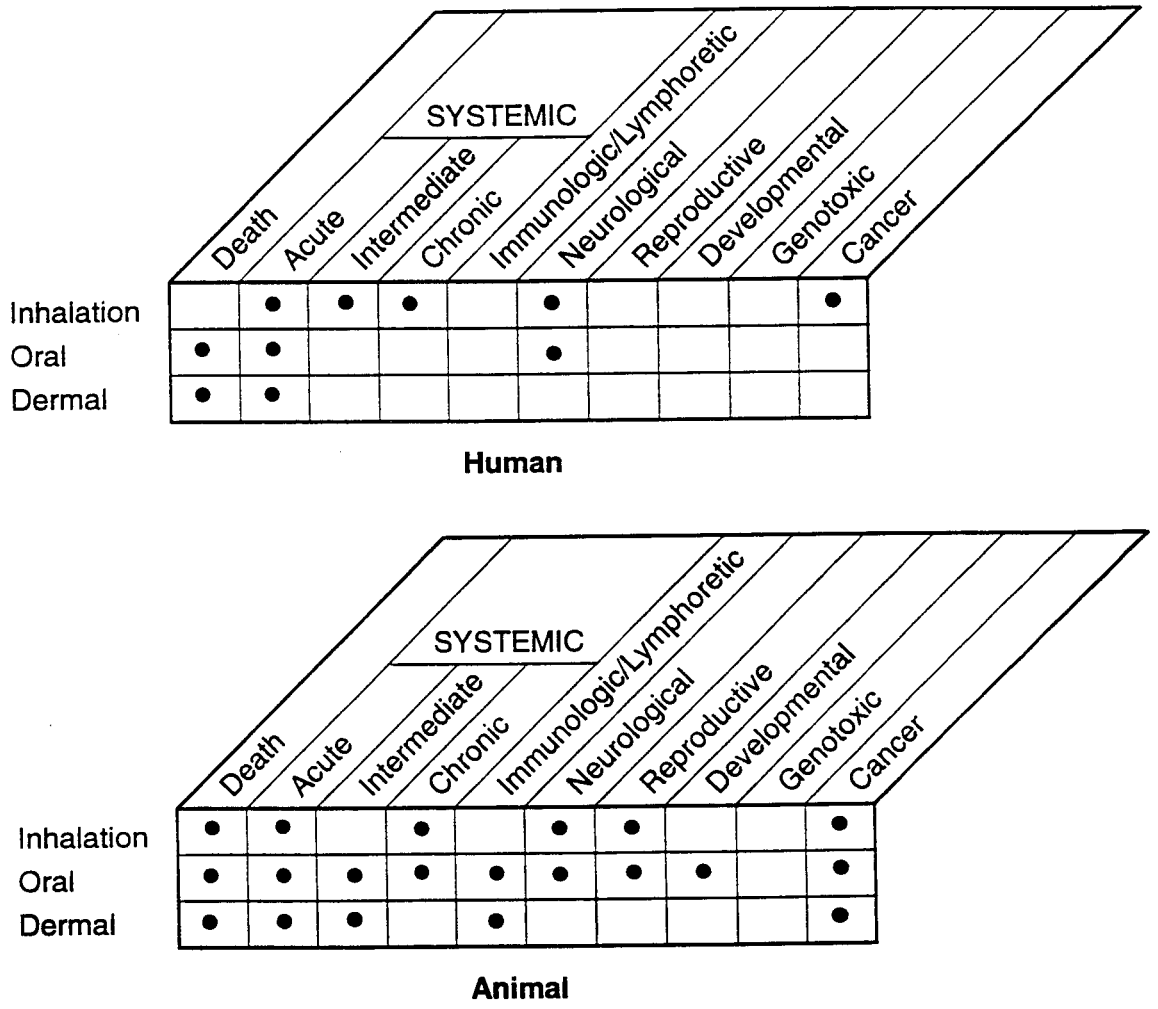
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene are summarized in Figures 2-4, 2-5, and 2-6.

The purpose of these figures is to illustrate the existing information concerning the health effects of naphthalene, l-methylnaphthalene, and 2-methylnaphthalene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As may be seen from the summary of existing studies shown in Figure 2-4, the data base on naphthalene toxicity in humans is not extensive. Data have been obtained from case reports of lethal or acute exposure, but these reports lack quantitative information on exposure levels. Animal data on naphthalene exist in several areas. Acute oral toxicity is well defined in several species, but inhalation and dermal data are minimal.

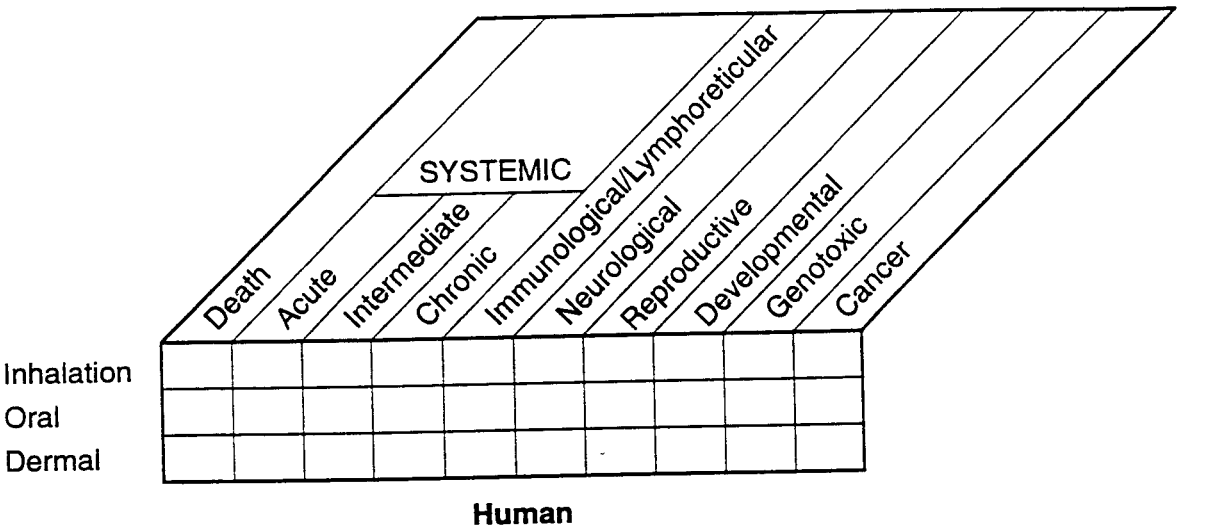
As can be seen from Figures 2-5 and 2-6, minimal information was located on the health effects of 1-methylnaphthalene or 2-methylnaphthalene in animals or humans via inhalation, oral, or dermal exposure. A few studies using intraperitoneal injection of 2-methylnaphthalene have been identified.

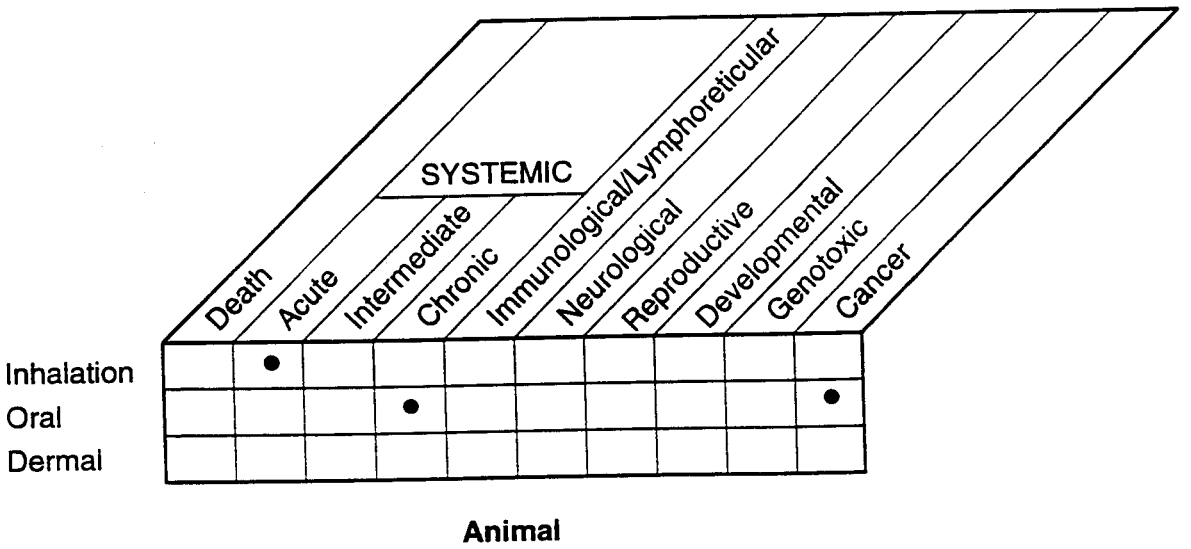
FIGURE 2-4. Existing Information on Health Effects of Naphthalene



● Existing Studies

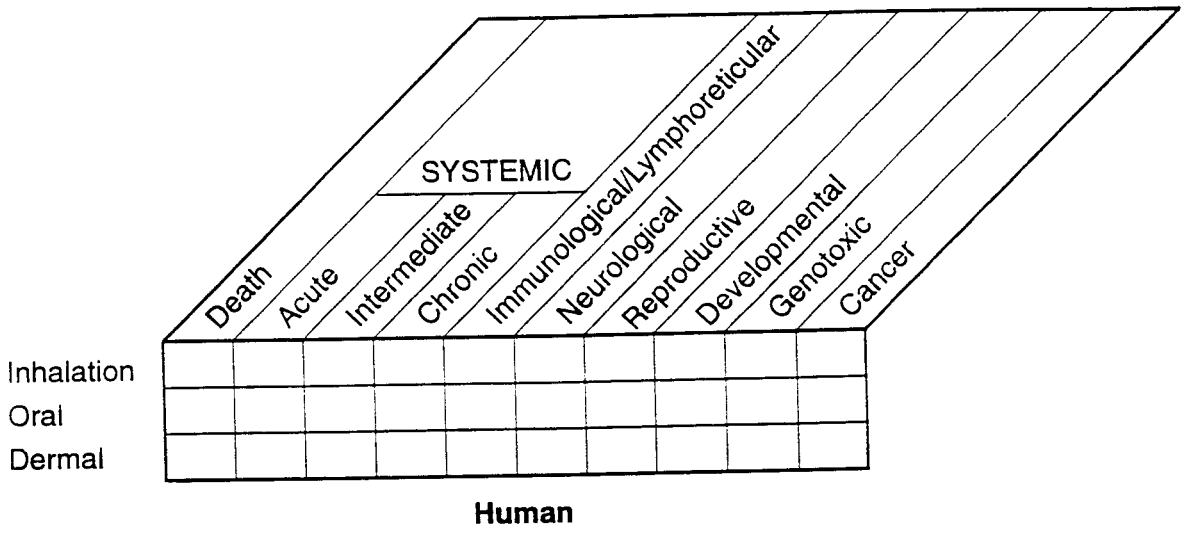
FIGURE 2-5. Existing Information on Health Effects of 1-Methylnaphthalene



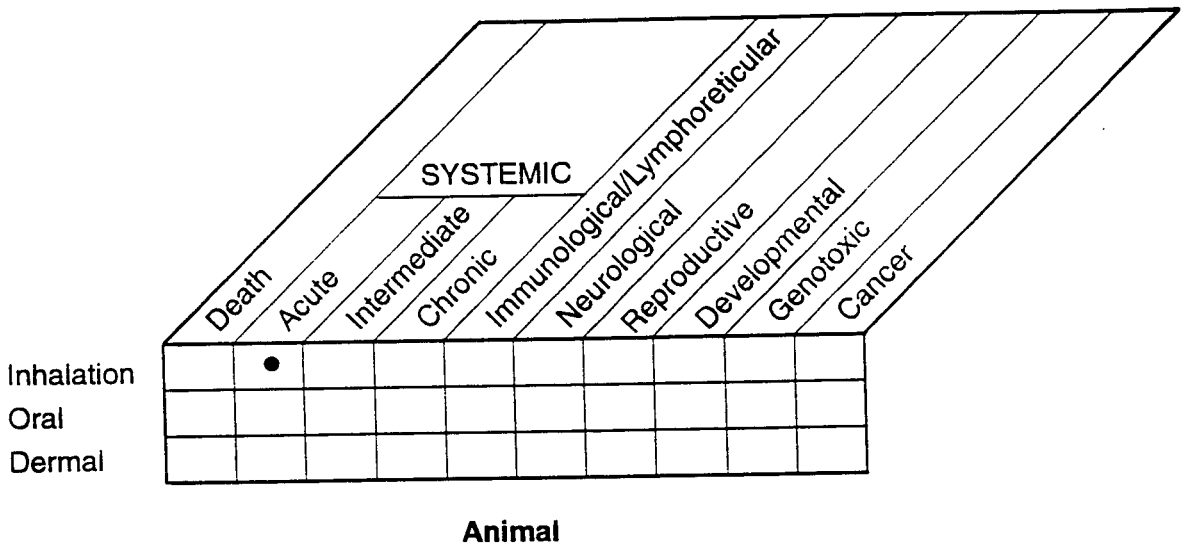


● Existing Studies

FIGURE 2-6. Existing Information on Health Effects of 2-Methylnaphthalene



Human



Animal

● Existing Studies

2.9.2 Identification of Data Needs

Acute-Duration Exposure. A number of reports of human exposure to acute inhalation, oral, or dermal doses of naphthalene have established the erythrocyte as the primary target (Dawson et al. 1958; Haggerty 1956; Kurz 1987; Linick 1983; MacGregor 1954; Mackell et al. 1951; Melzer-Lange and Walsh-Kelly 1989; Ojwang et al. 1985; Schafer 1951; Shannon and Buchanan 1982; Valaes et al. 1963). However, the data from these reports were not useful in predicting toxic or lethal dose levels by any of these routes because the exposure levels were not defined.

The acute oral toxicity of naphthalene has been studied in animals but there are no data for acute inhalation and dermal exposures. The most common adverse effects are ocular lesions (primarily cataracts). For the most part, these have been observed in rabbits (Srivastava and Nath 1969; Van Heyningen and Pirie 1967). Researchers have found short-term effects on respiration and alertness in rats after exposure to 50-450 mg/kg/day dietary naphthalene (NTP 1991a). This effect was used as the basis of the acute-duration oral MRL. Effects on liver (Rao and Pandya 1981) and lung (Shopp et al. 1984) weights have been reported, but no treatment-related histopathological lesions were observed. Lethal doses have been identified in mice (Plasterer et al. 1985; Shopp et al. 1984) and rats (Gaines 1969).

No data were suitable for the derivation of an acute-duration inhalation MRL. Hemolysis is the primary effect of acute naphthalene exposures in humans but not in rats or mice. Dose-response data for hemolysis from a susceptible animal species (such as dogs or the Jackson Laboratory ha [hemolytic anemia] mouse) are needed in order to obtain data that can be used to derive an MRL for humans. Both inhalation and oral exposure paradigms should be investigated.

No acute-duration studies are available on 1-methylnaphthalene or 2-methylnaphthalene exposure in humans using the inhalation, oral, or dermal routes. One study in animals was identified. This study showed that 1-methylnaphthalene (pure) administered in a kerosene aerosol was associated with increased reticulocyte and lymphocyte counts in splenectomized dogs and practical grade 1-methylnaphthalene was associated with increased leucocyte and neutrophil counts. Neither grade of 1 -methylnaphthalene had any affect on hematocrit values. The physiological significance of these findings is not apparent and the data are not suitable for use in derivation of an MRL for

1-methylnaphthalene. None of these parameters were affected when 2-methylnaphthalene aerosols were used.

Parenteral studies in animals revealed that a single intraperitoneal injection of 2-methylnaphthalene (1,000 mg/kg) was lethal in mice (Griffin et al. 1981). When a glutathione-depleting agent (diethyl maleate) was administered prior to administration of 2-methylnaphthalene, a lower dose of 2-methylnaphthalene (400 mg/kg) was also lethal. A single intraperitoneal injection of 1-methylnaphthalene (426 mg/kg) was not lethal in mice (Griffin et al. 1982). Systemic effects have been reported and were limited to effects on the respiratory system (Rasmussen et al. 1986). Exfoliation of the bronchiolar epithelium in mice was reported following a single intraperitoneal injection of 2-methylnaphthalene (Buckpitt et al. 1986; Griffin et al. 1981, 1983). A single intraperitoneal injection of 2-methylnaphthalene (1,000 mg/kg) did not cause liver or kidney lesions (6riffin et al. 1981, 1983). Because populations living near hazardous waste sites might be exposed to 1-methylnaphthalene or 2-methylnaphthalene for short periods, studies of acute exposure in animals by the inhalation and oral routes to determine potential target tissues and dose-related effects would be useful in assessing possible risk to humans.

Intermediate-Duration Exposure. Quantitative data were not provided in any intermediateduration inhalation case studies of human naphthalene exposure and, in one case, there was simultaneous exposure to para-dichlorobenzene (Harden and Baetjer 1978; Linick 1983). Limited data are available from animal studies in which the oral and dermal routes of administration were employed. Inhalation studies were not located. Ocular lesions (Rossa and Pau 1988; Van Heyningen and Pirie 1967; Yamauchi et al. 1986) and alterations in hepatic enzyme activities (Rao and Pandya 1981) and nitrogen metabolism (Shopp et al. 1984) were observed in animals following oral exposures to naphthalene for intermediate-durations.

There were no clear dose-response data for the cataractogenic effects of naphthalene in animals. Effects seen in animals at doses below the LOAEL for cataracts were inconsistent and often noted in only one sex. However, several results indicate that naphthalene exposure causes some impairment of hepatic function. The decrease in BUN and the BUN/creatinine ratio in female mice at a LOAEL of 5.3 mg/kg/day is the basis of the intermediate-duration oral MRL. No data were suitable for the development on an intermediate-duration inhalation MRL. Additional studies of the effects on

naphthalene on protein catabolism and the activity of urea cycle enzymes are needed to provide support for the oral MRL.

No intermediate-duration studies are available on 1-methylnaphthalene or 2-methylnaphthalene exposure in humans or animals using the inhalation, oral, or dermal routes. After single-dose intraperitoneal administration of 1-methylnaphthalene at 71 mg/kg, there was a minimal change in Clara cell vacuolization in mice (Rasmussen et al. 1986). The pulmonary effects of 2-methylnaphthalene were more severe than those for 1-methylnaphthalene, causing exfoliation of the lung epithelium with a dose of 200 mg/kg (Griffin et al. 1981).

The effects of the methylnaphthalenes on the lung epithelium following exposure by inhalation and oral routes need to be investigated to determine if there are changes in epithelial cell architecture accompanied by deficits in lung function and to identify the doses responsible for such changes. Because the lung tissue seems to be the tissue that is most sensitive to the methylnaphthalenes, studies using the inhalation route of exposure should precede those using the oral route.

Chronic-Duration Exposure and Cancer. There is one report of cataracts occurring in humans following chronic inhalation exposure to naphthalene (Ghetti and Mariani 1956) but no information on effects from exposures by the oral or dermal routes. The data in animals are limited to a 2-year inhalation study in mice (NTP 1992a) and a substandard 2-year oral study in rats (Schmahl 1955).

Chronic inflammation of the lungs as well as metaplasia of the olfactory epithelium and hyperplasia of the respiratory epithelium were reported at a dose of 10 ppm in a 2-year inhalation study in mice, but no effects on the eyes were observed (NTP 1992a). The data from this study were used to derive an MRL of 0.002 ppm for chronic inhalation exposure.

A chronic MRL for oral exposure was not derived because the data from the study by Schmahl (1955) were not comprehensive and did not provide a thorough examination of target tissues. A comprehensive chronic oral study of naphthalene, preferably in an animal species that is susceptible to hemolysis, is needed. Dose-response data for target systems (lens, liver enzymes, and hematological parameters) that can be used for determination of an MRL must be collected.

No epidemiological studies of tumor incidences in humans exposed to naphthalene have been conducted. If an appropriate population could be identified for study, tumor incidence data from occupationally-exposed individuals would be useful. Carcinogenicity data in animals are inconclusive.

Pulmonary adenomas and carcinomas were seen in female mice in a 2-year inhalation study, but not in male mice (NTP 1992a). Results were negative in a 2-year feeding study in rats (Schmahl 1955). Naphthalene does not appear to be mutagenic, but in instances where naphthalene-associated tissue injury causes hyperplasia, it may act as a tumor promoter rather than as a direct carcinogen. This hypothesis is supported by hyperplasia of the respiratory epithelium noted in the NTP mouse bioassay. Additional bioassay studies are not recommended at this time.

No chronic-duration studies are available on 1 -methylnaphthalene or 2-methylnaphthalene exposure in humans or animals using the inhalation or dermal routes. There is one oral chronic-duration study of 1-methylnaphthalene in mice that identified a LOAEL of 71.6 mg/kg/day for the occurrence of alveolar proteinosis in mice (Murata et al. 1993). This study was used as the basis of the oral MRL of 0.07 mg/kg/day for l-methylnaphthalene. In this same study, there was also a statistically significant increase in the incidence of pulmonary adenomas in males only. No corresponding data are available for chronic oral exposure to 2-methylnaphthalene.

Studies of biochemical and/or histological changes in the pulmonary epithelium of animals exposed to 1-methylnaphthalene by the inhalation route would provide useful information for individuals living near hazardous waste sites.

No epidemiological studies have been conducted in humans to establish a relationship between 1-methylnaphthalene or 2-methylnaphthalene exposure and cancer. Because populations living near hazardous waste sites can be exposed to these compounds for long periods, long-term animal bioassays of carcinogenicity would be useful.

The results observed with chronic oral exposure to l-methylnaphthalene (Murata et al. 1993), combined with the similar pulmonary effects of the two methylnaphthalenes in intraperitoneal studies (Rasmussen et al. 1986), are a strong justification for conducting chronic/cancer studies of these compounds.

Genotoxicity. There is limited evidence of genotoxic effects from naphthalene of in vitro mammalian test systems (NTP 1992a); however, results were negative in bacterial assays (Kraemer et al. 1974; McCann et al. 1975; NTP 1992a). Additional studies using an in viva mammalian system, such as the bone marrow micronucleus assay, would be of value.

Data in humans are limited to one study that reported no effects on human chromosomes in tests evaluating the effects of 1-methylnaphthalene or 2-methylnaphthalene on human peripheral lymphocytes in vitro (Kulka et al. 1988). 1-Methylnaphthalene and 2-methylnaphthalene were also determined to be nonmutagenic in 4 strains of *Salmonella typhimiurim* (Florin et al. 1980). Additional mutagenicity studies using an *in vivo* approach would be useful to confirm the apparent lack of 1-methylnaphthalene and 2-methylnaphthalene genotoxicity .

Reproductive Toxicity. No information is available on the reproductive effects of naphthalene in humans, although the occurrence of hemolytic anemia in the neonates of anemic, naphthalene-exposed mothers demonstrates that naphthalene and/or its metabolites can cross the placental barrier (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). No reproductive effects were observed in rabbits administered doses of up to 120 mg/kg/day by gavage or in rats given doses of up to 450 mg/kg/day during gestation, although doses of 150 mg/kg/day and greater were maternally toxic to rats.

There was a decrease in the number of live mouse pups per litter with a dose of 300 mg/kg/day given during gestation (Plasterer et al. 1985) and *in vitro* studies of naphthalene embryotoxicity in the presence of liver microsomes support the concept that naphthalene metabolites can be harmful to the developing embryo (Iyer et al. 1991). Thus, a one-generation study of naphthalene (corn oil gavage) is justified in order to clarify whether naphthalene is fetotoxic in the absence of maternal toxicity.

No studies are available on the reproductive toxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure. Examination of embryotoxicity and fetotoxicity (including evaluation of development effects) in a one-generation study following oral exposure to each of the methylnaphthalenes would demonstrate whether either compound has an effect on reproduction. The desirability of a study using the inhalation route of exposure can be evaluated once the results of the oral study are available.

Developmental Toxicity. There is no information on the potential developmental effects of naphthalene in humans, although, as mentioned previously, naphthalene and/or its metabolites can cross the placental barrier and cause hemolytic anemia in the fetus (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). Studies of the developmental effects of naphthalene in rats (NTP 1991a), mice (Plasterer et al. 1985) and rabbits (NTP 1992b; PRI 1985i, 1986) have been negative, except for a slight nonsignificant increase in fused sternebrae in female rabbit pups from a small number of litters at doses of 80 mg/kg/day and 120 mg/kg/day (NTP 1992b). The developmental component of the suggested one-generation study of naphthalene should be adequate for addressing developmental concerns. Additional developmental studies are not recommended.

No studies are available on the developmental toxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals following inhalation, oral, or derrnal exposure. The developmental component of the recommended one-generation study suggested above would be helpful in delineating whether or not the methylnaphthalenes are developmental toxins.

Immunotoxicity. There have been no comprehensive studies of the immunotoxicity of naphthalene in humans or animals using the inhalation, oral, or dermal exposure routes. The animal data from oral exposures indicate that naphthalene does not have an effect on humoral or cell-mediated immunity in mice (Shopp et al. 1984). Effects on the thymus and spleen were noted in mice and rats (Battelle 1980b; Shopp et al. 1984), but in no case were animals of both sexes affected. Because there are few data pertaining to the immunotoxicity of naphthalene, a battery of in vitro/in viva screening assays of immune function is recommended for determining whether more detailed and longer-term studies are needed.

No studies are available on the immunotoxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure. However, the dramatic increase in the level of monocytes in mice following long-term oral exposure to 1-methylnaphthalene (Murata et al. 1993) deserves additional study. The same battery of assays that is used for studying the immunotoxicity of naphthalene can also be used to determine if in-depth studies of the methylnaphthalenes are needed.

Neurotoxicity. The direct effects of naphthalene on the central nervous system have not been investigated in either humans or animals. Neurotoxic effects seen in humans exposed to naphthalene via inhalation or oral exposure appear to be a consequence of the diminished oxygen-carrying capacity of the blood which results from red cell hemolysis (Bregman 1954; Gupta et al. 1979; Kurz 1987; Linick 1983; MacGregor 1954; Ojwang et al. 1985; Zuelzer and Apt 1949). Clinical signs of neurotoxicity were only seen in one study of naphthalene in animals (NTP 1991a). This study used the oral route of exposure. Observed effects on respiration rate and alertness did not persist throughout the 10-day exposure period. This effect is the basis of the acute-duration oral MRL. The general lack of naphthalene neurotoxicity may reflect the hydrophilic nature of many of the naphthalene metabolites and resultant lack of affinity for the lipid-rich neurilemma. Examination of the external circumstances that promote neurotoxic effects in animals would provided support for the MRL.

No studies on the neurotoxicity of 1-methylnaphthalene or 2-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure were located. During the suggested acute- and intermediate-duration studies of the methylnaphthalenes, the animals should be observed for clinical signs of neurotoxicity. If there are no indications that these compounds are neurotoxic, additional testing is not justified.

Epidemiological and Human Dosimetry Studies. A small number of reports have equivocally suggested that workers exposed to naphthalene for long periods of time may have an elevated risk of cataract development (Ghetti and Mariani 1956; Lezenius 1902). This information, coupled with the cataractogenic effects of naphthalene in orally exposed rats (Kojima 1992; Xu et al. 1992b; Yamauchi et al. 1986) and rabbits (Rossa and Pau 1988; Srivastava and Nath 1969; Van Heyningen and Pirie 1967) in acute- and intermediate-duration studies, suggests that studies of occupationally-exposed workers would help to determine its potential to produce ocular toxicity in humans. The incidence of tumors, anemia, and reproductive problems in this population could be determined at the same time.

No epidemiological or human dosimetry studies on the effects of 1-methylnaphthalene or 2-methylnaphthalene were located. Exposure to these compounds, particularly through dermal contact or inhalation, can occur in workplaces where the compounds are produced or used. Populations living near hazardous waste sites can potentially be exposed by the oral, inhalation, and dermal routes. If an appropriate population can be identified, it would be helpful to conduct epidemiological studies to

determine if there are toxic effects (particularly on the Pungs) resulting from exposure to these substances.

Biomarkers of Exposure and Effect

Exposure. There are methods to determine the presence of naphthalene in adipose tissue and these methods have been used in a national monitoring program for the analysis of naphthalene in the adipose tissue of the general population (Stanley 1986). Metabolites of naphthalene, such as naphthols and naphthoquinones, have been detected in the urine of a patient 4 days after ingestion of naphthalene (Zuelzer and Apt 1949), but not in another patient at 17 days after ingestion (Mackell et al. 1951). 1-Naphthol is present in the urine of workers occupationally exposed to naphthalene. Maximum 1-naphthol levels occurred immediately after the end of the work period and in some cases had returned to baseline levels 8 hours later (Bieniek 1994). New immunological techniques are being developed for detecting urinary mercapturic acid naphthalene derivatives (Marco et al. 1993) and naphthalene/protein adducts (Cho et al. 1994a, 1994b). Additional work remains to be done in perfecting these techniques.

There is currently a method that can be used to measure levels of 2-methylnaphthalene in rat urine (Melancon et al. 1982). It would be useful to determine if this method can also be used with human urine. No methods were identified for measuring levels of 1-methylnaphthalene and its metabolites. The methodology used for detecting 2-methylnaphthalene and its metabolites should also detect 1-methylnaphthalene and its metabolites and is worth investigating.

Effect. There are no known specific biomarkers of effects for naphthalene, 1-methylnaphthalene, or 2-methylnaphthalene. Hemolytic anemia is commonly associated with human exposure to naphthalene, but may also be the result of exposure to other chemicals. The general clinical signs and organspecific effects of exposure to 1-methylnaphthalene or 2-methylnaphthalene have not yet been assessed using the inhalation, oral, or dermal routes. Once the acute- and intermediate-duration studies of exposure to 1-methylnaphthalene and 2-methylnaphthalene have been completed, the advisability of conducting studies for identifying biomarkers of effect can be reevaluated.

Absorption, Distribution, Metabolism, and Excretion. Although human absorption of naphthalene has not been quantitatively characterized, case reports indicate that humans can absorb toxicologically significant amounts of this compound by the oral, inhalation, or dermal routes (Bregman 1954; Chusid and Fried 1955; Dawson et al. 1958; Gidron and Leurer 1956; Gupta et al. 1979; Haggerty 1956; Kurz 1987; Linick 1983; MacGregor 1954; Mackell et al. 1951; Ojwang et al. 1985; Santhanakrishnan et al. 1973; Schafer 1951; Shannon and Buchanan 1982; Valaes et al. 1963; Zuelzer and Apt 1949). Laboratory animals such as rats, mice, and rabbits also absorb the chemical via their skin and gastrointestinal and respiratory tracts (NTP 1992; Rao and Pandya 1981; Shopp et al. 1984; Srivastava and Nath 1969; Turkall et al. 1994; van Heyningen and Pirie 1967). Indirect evidence has suggested that coadministration with oil enhances the rate and/or extent of both oral and dermal absorption of naphthalene (Plasterer et al. 1985; PRI 1986; Schafer 1951). Naphthalene adsorbed to organic-rich soils is absorbed across the skin more slowly than naphthalene from organic-poor soils (Turkall et al. 1994). The compound apparently partitions between the soil organic carbon and the hydrophobic components of the epidermis and dermis.

Information concerning the mechanism of absorption (facilitated versus passive transport) across the alveolar membranes, the gastrointestinal tract, and the skin would be useful. This information would be helpful in estimating the effect of dose on the absorption coefficient and the effect of the medium of exposure (water, oil, food, etc.) on absorption.

No data were identified concerning the distribution, metabolism, or excretion of naphthalene in humans or animals after respiratory exposure. Some data are available concerning distribution and excretion of orally ingested naphthalene and of naphthalene applied to the skin (Bakke et al. 1985; Eisele 1985; Mackell et al. 1951; Rozman et al. 1982; Summer et al. 1979; Turkall et al. 1994; Zuelzer and Apt 1949). The metabolism of naphthalene in different species has been investigated extensively using in viva and in *vitro* techniques (Bakke et al. 1990; Buckpitt and Richieri 1984; Buckpitt and Bahnson 1986; Comer and Young 1954; Homing et al. 1980; Kanekal et al. 1990; Mackell et al. 1951; Rozman et al. 1982; Stillwell et al. 1982; Summer et al. 1979; Wells et al. 1989; Zuelzer and Apt 1949).

In pigs, the tissue distribution of naphthalene varies with acute versus continual exposures (Eisele 1985). A smaller fraction of the label is found in the adipose tissues and kidney after continual naphthalene exposure than after a single dose. This is most likely the result of enzyme induction and

more rapid production of the hydrophilic, more easily excreted metabolites. The liver, lungs, and heart contain moderate amounts of naphthalene after single and repeated doses. Studies of the distribution of naphthalene and its metabolites in laboratory species (rats, mice, dogs, and rabbits) are needed for evaluating the species differences in toxicological effects"

No studies were located on the absorption, metabolism, and excretion of 1-methylnaphthalene in humans or animals following inhalation, oral, or dermal exposure. There was one study of 2methylnaphthalene in guinea pigs (Teshima et al. 1983). Parenteral studies in animals show that 2-methylnaphthalene is converted to both monohydrated compounds and dihydrodiols (Breger et al. 1981, 1983; Melancon et al. 1982). In addition, 2-naphthoic acid and the glycine or the cysteine conjugates were identified in rats (Melancon et al. 1982) and guinea pigs (Teshima et al. 1983). Studies by relevant exposure routes would further characterize the toxicokinetics of these compounds and would enhance the understanding of the potential risk associated with exposure to these compounds especially under circumstances where simultaneous exposure to both compounds occurs.

Comparative Toxicokinetics. Data suggest that there are strain- and species-specific effects associated with naphthalene toxicity. Laboratory animals, such as rats and mice, do not exhibit red cell hemolysis after exposure to naphthalene, while humans and dogs do (Battelle 1980a, 1980b; NTP 1992a; Shopp et al. 1984; Zuelzer and Apt 1949). There are differences in the pulmonary toxicity of naphthalene among mice, rats, hamsters, and guinea pigs that relate to the distribution of cytochrome P-450 enzymes in the tracheobronchial tree (Plopper et al. 1992a, 1992b) as well as differences in the susceptibility of rats and mice to the cataractogenic properties of naphthalene (Wells et al. 1989). The strain of mice (i.e., C57BW6 versus DBA/2) also influences the tendency for cataract formation following exposure to naphthalene (Wells et al. 1989). These differences are all hypothetically related to species differences in naphthalene metabolism. Further evaluation of these differences and comparative studies of distribution and metabolic patterns would be helpful in identifying an appropriate animal model to study the effects found to be the most relevant to humans.

There are no data available concerning the toxicokinetics of 1-methylnaphthalene or 2-methylnaphthalene in humans following inhalation, oral, or dermal exposure. There are no data from studies of 1-methylnaphthalene in animals, but there are limited data for 2-methylnaphthalene (Breger et al. 1983; Griffin et al. 1982; Melancon et al. 1982, 1985; Teshima et al. 1983). Initially,

studies are needed that evaluate toxicokinetic parameters in several animal species to identify an appropriate model for extrapolating those results to humans.

Methods for Reducing Toxic Effects. Available methods are sufficient for reducing peak absorption of naphthalene following ingestion (Melzer-Lange and Walsh-Kelly 1989; Siegel and Wason 1986; Stutz and Janusz 1988). No antidotal methods are available that would be useful for treatment of naphthalene exposure based on any proposed hypothesis pertaining to the mechanism of action. Additional studies to characterize the metabolic activation of naphthalene and the role of circulating reactive intermediates from nontarget tissues may be useful in developing methods for interfering with the mechanism of action. Further studies to identify ways to reduce or prevent accumulation in the target tissue are warranted.

There are no compound-specific methods for reducing the toxic effects of 1-methylnaphthalene and 2-methylnaphthalene. Additional information on the toxicokinetics and mechanism of action for these compounds would be beneficial in identifying possible approaches for reducing compound toxicity.

2.9.3 On-going Studies

A study is being conducted by G. S. Yost, University of Utah, to evaluate the toxicity of 2-methylnaphthalene on the lungs. The study will utilize chemical, biochemical, cellular, isolated organ, and whole animal techniques to evaluate the bioactivation and detoxification mechanisms. Another study is being conducted by R. E. Billings, University of Nevada, and involves the role of naphthalene- 1,2-catechol in the pulmonary toxicity of naphthalene and its toxicity in isolated rat liver cells, in perfused liver, and in the intact animal. These studies are being sponsored by the National Institutes of Health. In addition, the National Toxicology Program is planning to conduct a-year carcinogenicity/toxicity studies in F344 rats.